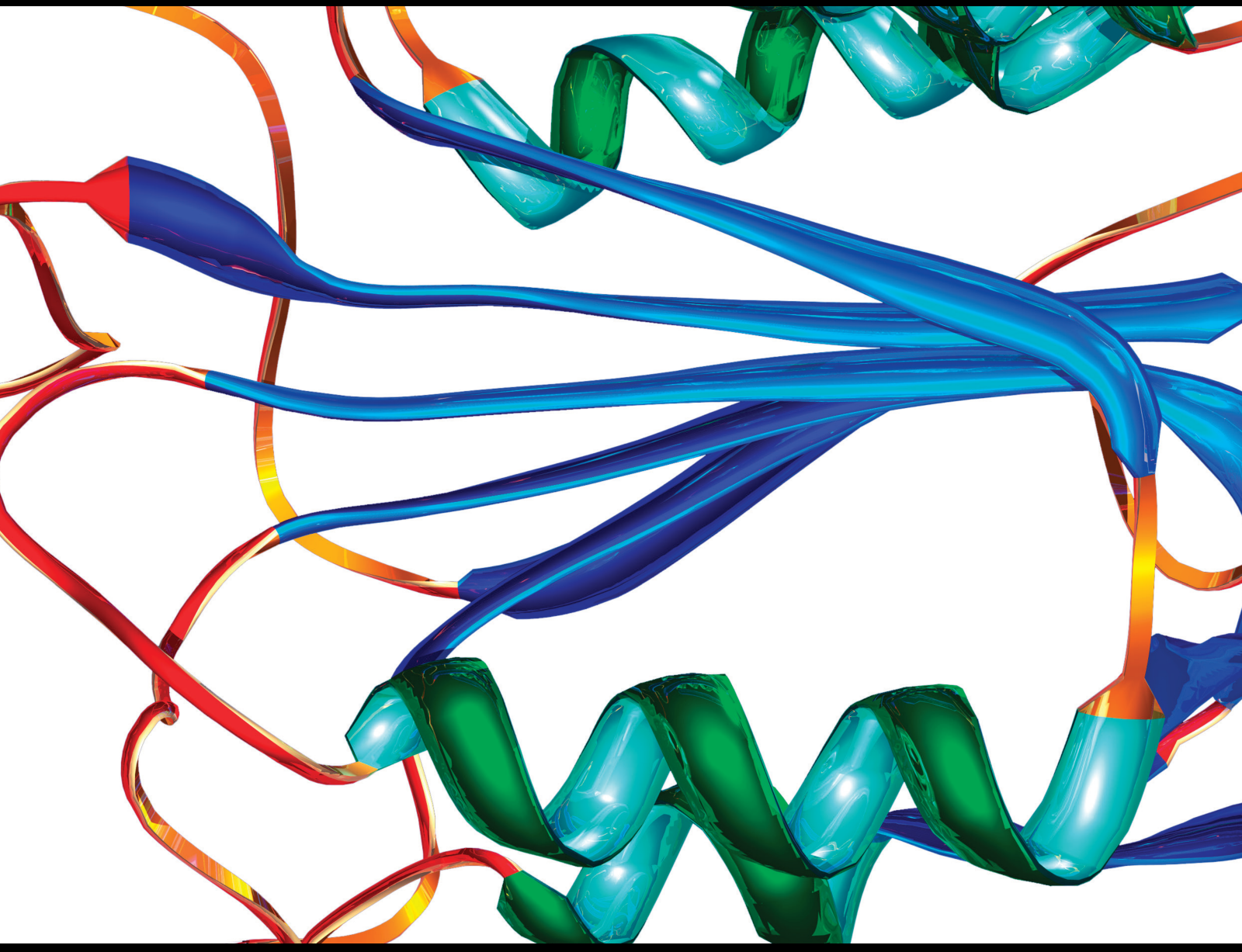
Disease Markers

Biological and Imagistic Markers of Cardiovascular Toxicity in Cancer Treatments

Lead Guest Editor: Anca Daniela Farcas
Guest Editors: Mihaela Mocan, Nicole Sekarski, Simona Sorana Cainap, and Andrada Pârvu



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Research Article

Validation of Normal P-Wave Parameters in a Large Unselected Pediatric Population of North-Western Romania: Results of the CARDIOPED Project

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Aims. Reference values of the P-wave on 12 lead electrocardiograms are lacking for children and adolescents in Eastern Europe. Hence, the present study is aimed at determining the standard values of the P-wave in children and adolescents based on ECG data from the CARDIOPED project, a large-scale general population of children who participated in a screening program in Transylvania, Romania. *Methods and Results*. A total of 22,411 ECGs of participants aged 6 to 18 years old from a school-based ECG screening were obtained between February 2015 and December 2015 in Transylvania, Romania. Three pediatric cardiologists manually reviewed each ECG. P-wave duration, voltage, axis, and correlation with gender and age were analyzed. The mean P-wave duration was 88 ± 10.7 ms, with a maximum duration of 128 ms. P-wave showed a positive correlation with age but did not differ between sexes. There was a positive correlation between the P-wave duration and the heart rate, but not with the body max index. The mean P-wave axis was 40.4 ± 31.1, and the mean P-wave amplitude was 0.12 ± 0.03 mV. *Conclusion*. In this study on many pediatric subjects, we have provided normal limits for the P-wave in Romanian children aged 6-18 years. Our findings are useful for creating interpretation guidelines for pediatric ECG.

1. Introduction

A correct interpretation of electrocardiograms in children relies on comparison with standard values derived from the normal population. Comprehensive data on ECG in Romania are lacking. No study to date explores P-wave characteristics in Eastern Europe and, more specifically, in Romania. Romania is a south-eastern country of Europe and a state member of the European Union. It shares borders with Hungary, Serbia, Bulgaria, Ukraine, and the Republic of Moldova. It covers 238,397 km^2 and has 19.71 million inhabitants with a median age of 40.9 years. ECG interpretation depends on knowledge of normal limits, which in children are age-dependent. Diagnostic ECG criteria require the availability of appropriate normal references.

A P-wave duration of more than 110 ms was associated in adults with left atrial enlargement, electromechanical dysfunction, atrial fibrillation, and embolic stroke [1–6].

In pediatrics, the currently accepted "normal" P-wave is 70 ms for infants and 90 ms for children [7, 8].

Our study is aimed at determining the P-wave's standard values in a large nonselected population of healthy children from North-Western Romania.

2. Material and Methods

The study population consisted of 23,833 healthy children consecutively recruited from the primary schools of North-West of Romania. We eliminated 1422 ECGs because of ECG limb lead reversal, inappropriate attachment of electrical leads, artifacts/drifts, ectopic atrial rhythms, or junctional rhythm. In consequence, 22,411 ECS were considered for the final analysis. Twelve primary schools randomly selected from 64 schools in Transylvania were approached for participating in this study. Ethical permission was granted by the Ethics Committee of the "Iuliu Hatieganu" University of Medicine and Pharmacy and agreement from the schools, head teachers, school nurses, generalists, and parents of the children. Written consent from the parents was obtained. They were told that the project was aimed at estimating the frequency of cardiac disease in school children. They were asked to complete some demographic data like weight, height, urban or rural area of living, and parents' cardiac disease. No children had a history of cardiovascular disease, and none received medication. All 22,411 children had a normal physical examination.

All children underwent a 12-lead digital ECG recording using 20 machines BTL-08 MT Plus at a sampling rate of 2000 Hz. The frequency response of this recorder is flat to 170 Hz. ECGs were analyzed by 200 physicians (cardiologists or pediatricians) for three months and manually reviewed by 3 cardiac pediatricians for three years. The onset and the offset of the P-wave were defined as the junction between the P-wave and the isoelectric line before and after the wave's start. Amplitude measurements of the P-wave were made using the PR segment as the baseline. The 200 physicians could compare the values manually obtained from magnified ECG tracing on the monitor with the computer program's values on the digitized ECG. When there was a difference between manual and computer measurement, the manual value was selected for further statistical analysis.

2.1. Statistical Analysis. Continuous variables are expressed as mean ± standard deviation and were compared with the two-sided Student test (t-test). Categorical variables are expressed as counts or percentages and were compared using the chi-square test. Linear regression analysis was used to test the prediction of P-wave duration by age and heart rate. Multiple imputations were used for the missing data. A p value of < 0.05 was considered statistical significance. All statistical analyses were performed using the SPSS 23.0 software (SPSS In. Chicago, IL, USA).

2.1.1. Dealing with Missing Data. Among the 22,411 children used in cross-sectional analyses, there were small amounts of missing data for height, weight, and P-wave characteristics. These data varied from 0 (e.g., for child age and gender) to 4% (for the P-wave duration, amplitude, and axis) and 8% (for weight, height, and BMI where the parents offered data). We used multiple imputations for the missing data to increase power and minimize selection bias in our findings.

3. Results Population

Demographic characteristics are presented in Table 1. In brief, they were 22,411 children with ages ranging from 6 to 18 years old (corresponding to the eight grades of primary school), weight from 16 to 135 kg, height from 39 to 207 cm, and BMI from 14 to 50 kg/m^2.

Of the 22,411 children, 22,349 had normal sinus rhythm. Heart rate ranged from 45 to 168, with a mean of 88.2 ± 11.5 bpm. The mean QRS axis was 62.1 ± 29.3° with the axis being 0 to 120° in 96.4% of the children. The mean PR interval measured 144.8 ± 24.5 ms. The mean QRS duration was 81.3 ± 10.8 ms with 99.9% of the children having a QRS duration of <120 ms. The mean QT duration was 408 ± 27.9 ms.

3.1. P-Wave Description. The mean values of P-wave duration were 88.2 ms with a minimum of 50 ms and a maximum of 128 ms (Table 1). P-wave duration was correlated to age ($r = 0.075$, $p < 0.001$), indicating a progressive increase of P-wave duration with increasing age (Figure 1). There was no significant difference between sexes (88.0 ± 10.6 ms in boys vs. 87.8 ± 10.6 ms in girls, $p = 0.051$). Furthermore, P-wave duration showed a statistically significant correlation with heart rate ($r^2 = -0.095$, $p < 0.001$) (Figure 2), age ($r^2 = 0.075$ with $p < 0.001$), weight ($r^2 = 0.044$ and $p < 0.015$), and height ($r^2 = 0.063$ and $p < 0.001$) but not with the BMI ($r^2 = 0.022$; $p = 0.216$).

The 95th and 99th percentiles for the P-wave duration were 106 and 120, respectively (Table 2). The 95th and 99th taken as the upper limit of normal are arbitrary cut-off values frequently used in the pediatric population for hypertension, obesity, electrocardiogram, or echocardiogram parameters. The 2nd percentiles, taken as the lower limits of normal, were 66 ms (Figure 3).

Using the 90 ms cut-off value for increase duration of the P-wave, 31% of our population would have been classified as having an increased value.

The amplitude of the P-wave was 0.12 ± 0.03 mV with a range between 0 and 0.25 mV. We did not find a significant association between P-wave amplitude and heart rate, sex, age, weight, height, and BMI (all p values > 0.05).

P-wave axis was measured using the positive or negative deflections in all 6 limb leads and calculating the direction of electric activity on the hexaxial reference system. P-wave axis had a mean of 40.4 ± 31.1°. There was no correlation between the P-wave axis and other variables like heart rate, age, sex, weight, height, and BMI.

4. Discussion

Standards of normal values for ECG interpretation in normal children have been available since 1979 [9]. Davignon et al. recorded 2141 ECGs in children from Quebec, Canada, and

Table 1: Patient characteristics.

Parameter	
N	22,411
Age (years; mean ± SD)	12.4 ± 3.1
Gender (male; *N* %)	10,712 (47.8%)
Age distribution	
6-7 years	48 (0.2%)
7-8 years	1237 (5.6%)
8-9 years	1771 (8.0%)
9-10 years	1806 (8.2%)
10-11 years	2075 (9.4%)
11-12 years	2314 (10.5%)
12-13 years	2080 (9.4%)
13-14 years	2079 (9.4%)
14-15 years	2082 (9.5%)
15-16 years	2224 (10.1%)
16-17 years	1940 (8.8%)
17-18 years	1580 (7.2%)
18 years	792 (3.6%)
Heart rate (bpm; mean ± SD)	88.2 ± 11.5
Mean P-wave duration (ms; mean ± SD)	88.0 ± 10.7
Mean P-wave axis (grades; mean ± SD)	40.4 ± 31.1
Mean P-wave amplitude (mV; mean ± SD)	0.12 ± 0.03
Weight (kg; mean ± SD)	49.1 ± 16.8
Height (cm; mean ± SD)	154.8 ± 16.0
BMI (kg/m^2; mean ± SD)	20.0 ± 4.0

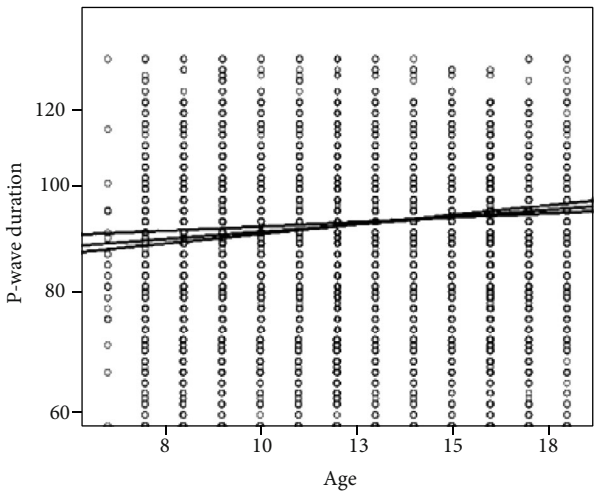

Figure 1: The positive correlation between the P-wave duration and the age (scatterplot with regression line; standardized beta coefficient = 0.095; $p < 0.000001$).

developed graphs and tables of normal values for future use when evaluating ECG in pediatric population. Recent studies suggest that some of these cut-offs should be reviewed and maybe revised to consider the newer research on larger populations of children, as possible physiological changes in children and races that might have appeared since the original paper was published.

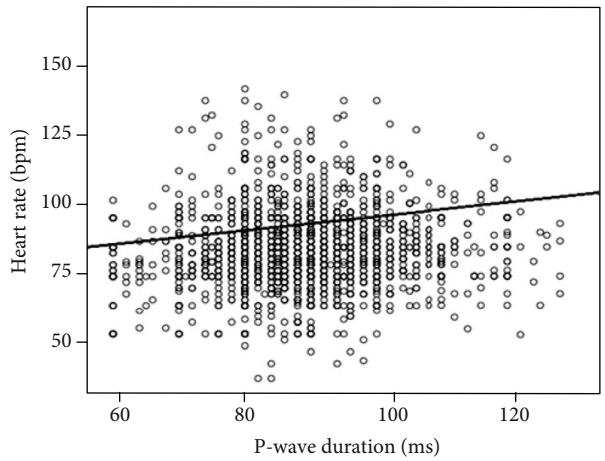

Figure 2: The positive correlation between the P-wave duration and the heart rate (scatterplot with regression line; standardized beta coefficient = 0.08; $p < 0.000001$).

Macfarlane et al. [10] showed that the 98th percentile of the normal amplitude in children could be out of range in 46% of patients when compared with values obtained by Davignon et al. Furthermore, Rinjbeeck et al. [11] showed on European population the differences in normal values when compared with those obtained by Davignon and Macfarlane. Older normal limits may no longer apply to current pediatric practice [12].

In 1990, the American Heart Association recommended a minimum of 500 Hz which has been recommended for sampling rate in adult ECG [13]. As for pediatric ECGs, higher sampling rates should be used [8, 14]. In the study of Davignon et al., ECGs were recorded at a sampling rate of 333 Hz. Later, Macfarlane et al. used a sampling rate of 500 ms and found that 46% of the amplitude measurements were beyond the cut-off values recommended by Davignon. Our study applied a sampling rate of 2000 Hz, which was considered sufficiently high to record a pediatric ECG accurately.

In a study on 232 healthy children, Kose et al. [15] demonstrated that the increase in P-wave duration corresponded to age increase in a cohort aged 7 to 15 years. In a later study [16], P-wave duration was also associated with age in hospitalized children, with the most significant increase occurring at >10 years of age. In the study of Loo et al. [16], the prevalence of large P-waves compared to the cut-off of 90 ms is particularly high (27%) and in opposition with the low percentage of atrial arrhythmias in this pediatric group.

Investigations on African population [17] found a P-wave duration of 70 ms in a cohort of 1500 children aged 0 to 12 years. Probably, the difference compared to our values comes from the fact that we also included children \between 12 and 18 years. It is well known that the duration of the P-wave increases with age, which is why in our study, the average duration of the P-wave was 88.2 ms which is higher compared to the value found on the Nigerian population.

Table 2: The 95th and the 99th percentile of the P-wave duration, amplitude, and axis.

Number of patients = 22,411	95th percentile	99th percentile
P-wave duration	106	120
P-wave amplitude	0.18	0.25
P-wave axis	75	96

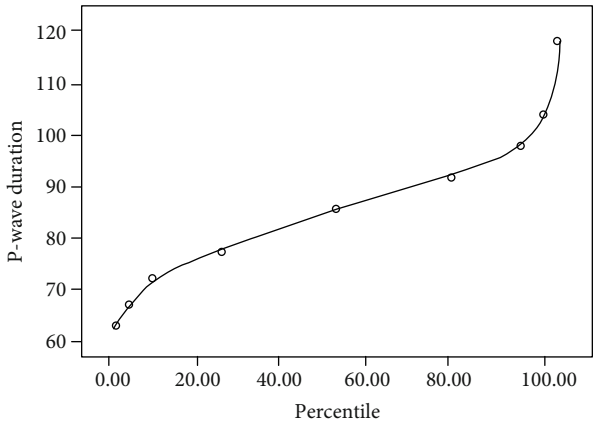

Figure 3: Second, 10th, 25th, 50th, 75th, 95th, and 98th percentiles for the P-wave duration.

A study performed in Turkey on children up to 16 years of age found an average P-wave duration of 64 ms in girls and 62 ms in boys. Besides the fact that this study included a 10-times smaller number of children compared to our study, it also included newborns, infants, and children aged 1 to 6 years. We believe that the difference with our results is due to a shorter duration of the P-wave in newborns and infants, as the P-wave duration is shorter in smaller ages [18].

Another European study [11], similar to ours, was performed on Dutch population and obtained values for the P-wave duration higher than ours: 92 ms for the age group 5-8 years, 98 ms for 8-12 years, and 100 ms for 12-16 years. In Rinjbeck's study, the weight and height of the children are not specified. It is possible that the differences observed between the 2 studies in the duration of the P-wave are related to the difference in weight and height between the Dutch [19] and the Romanian population [20].

Research performed on American population [21] found P-wave duration values similar to our values in Caucasian individuals. On the other hand, African-American individuals had a longer P-wave duration compared to ours, and also higher than the values found in African individuals in the study of Kolawole et al.

ECG recordings on a Japanese population of children found P-wave duration values similar to those recorded in our group of Caucasian children: 77 ms for 1st graders, 87 ms for 7th graders, and 99 ms for 10th graders. There were no significant differences in age or sex distribution between our study and that of Yoshinaga et al. [22]. The number of children was high in both studies.

Prolonged P-wave duration has been described with different pediatric medical conditions. One of the most important pediatric pathology remains cancer, where excellent long-term survival could raise more problems such as chemotherapy induced cardiomyopathy [23]. Ozmen et al. [24] compared 43 pediatric patients with pulmonary stenosis to 33 healthy pediatric controls and showed increased P-wave duration in the first group. Furthermore, Ho et al. [25] compared 94 children with ostium secundum atrial septal defect with healthy children. They observed an increase in the mean P-wave duration in patients with the atrial septal defect. Wong et al. [26] also demonstrated an increase in the P-wave duration in patients with Fontan surgery compared to healthy children matched for age and sex. Also, the P-wave's increased duration was noted in patients with tetralogy of Fallot [27] and viral infections [28, 29]. Probably, the 90 ms value is correct for children who have congenital heart disease or atrial arrhythmias. But for healthy children, the cut-off value should be revised.

The interatrial block in adults is defined as a prolongation of the P-wave >110 ms on standard 12-lead ECG. In children, cut-offs for P-wave durations are lower, 90 ms, due to reduced myocardial mass in the pediatric population. However, in children, an increase in P-wave duration is, in fact, proportionate to age. In our study, we found that the duration of the P-wave in healthy children had a mean of 88.0 ms and was positively correlated to age; therefore, it increases with the age of the individual, as reported earlier [24]. Thirty-one percent of our population would have been classified as having an increased value when using the 90 ms cut-off to increase the P-wave duration. The 95th and 99th are arbitrary cut-off values frequently used in the pediatric population for electrogram characteristics and hypertension, obesity, and echocardiogram values. The 95th and 99th percentiles for the P-wave duration in our pediatric population were 106 and 120, respectively; therefore, the 90 ms cut-off value proposed for the interatrial block in the pediatric population should be reconsidered.

5. Limitations

Our physicians used manual P-wave measurements on a magnified screen image. Magnification of ECGs on a high-resolution screen may differ from manual measurements on paper-printed ECGs but can save time. All ECGs were analyzed for three months.

6. Conclusion

In this study on a large unselected pediatric population, we have provided limits for the P-wave in Romanian children aged 6-18 years. The mean P-wave duration was 88 ± 10.7 ms, with a maximum duration of 128 ms. P-wave duration showed a positive correlation with age and heart rate.

Data Availability

The data used to support the findings of this study are included within the article.

Conflicts of Interest

The authors declare no conflict of interest.

Acknowledgments

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Review Article

Assessment and Management of Cardiotoxicity in Hematologic Malignancies

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With the increasing overall survival of cancer patients due to recent discoveries in oncology, the incidence of side effects is also rising, and along with secondary malignancies, cardiotoxicity is one of the most concerning side effects, affecting the quality of life of cancer survivors. There are two types of cardiotoxicity associated with chemotherapy; the first one is acute, life-threatening but, fortunately, in most of the cases, reversible; and the second one is with late onset and mostly irreversible. The most studied drugs associated with cardiotoxicity are anthracyclines, but many new agents have demonstrated unexpected cardiotoxic effect, including those currently used in multiple myeloma treatment (proteasome inhibitors and immunomodulatory agents), tyrosine kinase inhibitors used in the treatment of chronic myeloid leukemia and some forms of acute leukemia, and immune checkpoint inhibitors recently introduced in treatment of refractory lymphoma patients. To prevent irreversible myocardial damage, early recognition of cardiac toxicity is mandatory. Traditional methods like echocardiography and magnetic resonance imaging are capable of detecting structural and functional changings, but unable to detect early myocardial damage; therefore, more sensible biomarkers like troponins and natriuretic peptides have to be introduced into the current practice. Baseline assessment of patients allows the identification of those with high risk for cardiotoxicity, while monitoring during and after treatment is important for early detection of cardiotoxicity and prompt intervention.

1. Introduction

Due to the advancement in cancer treatment in the last years, the overall survival of cancer patients increased significantly. Unfortunately, this has also led to increased exposure to side effects of different treatment modalities. One of the most important side effects with a major impact on survival is cardiac toxicity. Therefore, a multidisciplinary approach of these patients is necessary, in order to find a balance between the response to treatment and cardiovascular morbidity and mortality. Development of protocols for prevention and early treatment of cardiotoxicity can avoid chemotherapy withdrawal and optimize outcomes [1]. In this article, the authors aimed to review the most important cardiotoxic therapies used in hematologic malignancies, describe their mechanism of action, and summarise the imagistic and laboratory methods used for monitoring cardiotoxicity, highlighting the importance of early detection and intervention.

2. Therapies with Cardiotoxic Potential

Drugs with cardiotoxic potential have been classified into two groups: type I agents, which cause a dose-dependent and mainly irreversible cardiotoxicity (e.g., anthracyclines), and type II agents, whose cardiotoxicity is not dose dependent and mainly reversible (e.g., tyrosine kinase inhibitors, immunomodulatory drugs, and proteasome inhibitors) [2].

3. Mechanism of Cardiotoxicity

3.1. Cardiotoxicity of Anthracyclines. Anthracyclines are antibiotic antineoplastic agents discovered in 1963 and well known for their cardiotoxic effect. Doxorubicin and daunorubicin are two members of this class. Anthracycline-induced cardiotoxicity can have two forms:

(a) Early or acute, which may manifest as arrhythmia, myocarditis, pericarditis, or acute left ventricular failure; these complications resolve after withdrawal of treatment. This type of anthracycline-induced cardiotoxicity is more common in the elderly, probably due to underlying heart disease, and also in patients with large single doses of doxorubicin

(b) Late or chronic cardiomyopathy, with late onset of arrhythmia and ventricular dysfunction; this type of cardiotoxicity is related to the cumulative dose of doxorubicin. Studies have demonstrated that the estimated cumulative incidence of congestive heart failure was 5% at a cumulative dose of 400 mg/m^2, 26% at a dose of 550mg/m^2, and 48% at a dose of 700 mg/m^2 [3, 4]

3.1.1. Mechanism of Anthracycline-Induced Cardiotoxicity. Generally, cardiotoxicity is caused by myocardial cell loss, apoptosis, and necrosis, mediated by oxidative stress, but the exact mechanism of anthracycline-induced cardiotoxicity is not known. There are four proposed hypotheses:

(a) Iron and free radical theory, in which oxidative stress is involved due to depletion of endogenous antioxidant

(b) Metabolic hypothesis, in which an alcoholic anthracycline metabolite interferes with the myocardial energy pathway and intracellular calcium concentration

(c) Unifying hypothesis, in which an alcoholic anthracycline metabolite also causes increased calcium concentration in the myocardial fiber and damages it

(d) Apoptosis hypothesis, in which there is an upregulation of proapoptotic markers [5]

3.2. Cardiotoxicity of Cyclophosphamide. Cyclophosphamide is an alkylating agent which can cause cardiotoxicity shortly after therapy, due to a toxic effect of its metabolite on the endothelial cells. It can cause myopericarditis and myocardial necrosis and also pulmonary hypertension [5].

3.3. Cardiotoxicity of Tyrosine Kinase Inhibitors. Tyrosine kinase inhibitors (TKIs) have revolutionised cancer therapy, especially that of chronic myeloid leukemia. They bind to the adenosine triphosphate (ATP) binding pocket of the tyrosine kinase and transfer a phosphate group from ATP to a tyrosine residue. TKIs inhibit not only the malignant cells but also the nonmalignant cells as well, and this explains their side effects. The most common side effects are rush and diarrhea, but they also may cause cardiotoxicity. Cardiotoxicity of TKIs ranges from asymptomatic QT prolongation to decreased LVEF (left ventricular ejection fraction) and congestive heart failure, acute coronary syndrome and myocardial infarction, arterial thrombosis, and hypertension. Because of the need for long-term use of these agents, understanding the mechanism of cardiotoxicity and knowing which have cardiac toxicity are important [6].

(a) Imatinib targets Bcr-Abl, c-Kit, and PDGFR. Known side effects of Imatinib are peripheral edema, shortness of breath, and fatigue. Cardiotoxicity of Imatinib is controversial; several studies have observed no statistical differences between those treated with or without Imatinib; however, peripheral edema was more frequent in the Imatinib arm [7]

(b) Dasatinib targets Bcr-Abl, c-Kit, PDGFR, and Src family of kinases. Evidence of cardiotoxicity was seen early in clinical trials; in particular, pleural effusion and peripheral edema were described. The DASISION trial, which included 258 patients, one arm treated with Imatinib and the second with Dasatinib, has demonstrated significantly higher rate of pleural effusion and pulmonary hypertension in the Dasatinib arm [7]

(c) Nilotinib is an inhibitor of Bcr-Abl, c-Kit, and PDGFR. It can cause QT prolongation, leading sometimes to torsade de pointes. Ischemic heart disease is another complication shown in a clinical trial. After an average time on nilotinib therapy of 60 months, the incidences of ischemic heart disease-related cardiac events in the nilotinib 300 mg arm and 400 mg arm were 9.3 and 15.2%, respectively [7, 8]

(d) Ponatinib has the highest risk of cardiotoxicity from the TKIs, including congestive heart failure, cardiac arrhythmias, and hypertension. In the phase 2 ponatinib CML evaluation trial, ponatinib was shown to have dose-dependent cardiotoxicity in 267 evaluated patients. Among the ponatinib-treated CML patients participating in clinical trials, 31% reported arterial occlusive events in the 5-year follow-up. Additionally, 4% of patients reported cardiac adverse events of atrial fibrillation (AF) and 3% angina pectoris [8]

3.4. Cardiotoxicity of Immunomodulatory Drugs (IMIDs). IMIDs are part of many multiple myeloma regimens, often in combination with other potentially cardiotoxic drugs, like proteasome inhibitors (PI). Both arterial and venous thrombotic events are described in association with IMIDs. The mechanisms of these side effects are direct damage of the endothelial cells, increased platelet aggregation, and higher von Willebrand factor levels [9]. Data from two phase III trials comparing combination of lenalidomide and dexamethasone to dexamethasone alone demonstrated an increased incidence of myocardial infarction and cerebrovascular events (1.98% and 3.4% vs. 0.57% and 1.7%, respectively) in the lenalidomide arm. Therefore, all patients should receive thromboprophylaxis with aspirin or, in case of high risk,

anticoagulants [10]. IMIDs may also induce arrhythmias, like bradycardia or atrioventricular block, with thalidomide being associated to sinus bradycardia in 5% of patients [9, 11].

3.5. Cardiotoxicity of Proteasome Inhibitors. Proteasome inhibitors (PI) represent the backbone of multiple myeloma therapy. Inhibition of proteasomes induces apoptosis of the cells due to the aberrant proteome.

(a) Bortezomib is a first-generation PI. A systematic review and meta-analysis of cardiovascular adverse events (CVAE) in patients treated with Bortezomib showed a 3.8% rate of all-grade CVAE. However, randomised studies did not find a significantly higher risk of CVAE in the Bortezomib arm compared to the control arm [9]

(b) Carfilzomib is an irreversible proteasome inhibitor approved in 2012, and since then, there are increasing reports of carfilzomib-associated CVAE, including heart failure, hypertension, arrhythmias, ischemic events, and cardiac arrest. Possible mechanisms for these side effects are oxidative stress on myocardiocytes, endothelial effects, and an increased coronary vascular tone and reactivity. A meta-analysis of 24 prospective studies, including 2594 patients with multiple myeloma, showed a rate of all-grade CVAE of 18.1% and high-grade CVAE of 8.2%. Heart failure (4.15%) and hypertension (12.2%) were the most common side effects, while arrhythmias and ischemic events were less common. Higher doses of carfilzomib were associated with higher rates of CVAE [9]

(c) Ixazomib is an oral analog of Bortezomib, reversibly inhibiting the proteasome and the NFKB pathways in myeloma-supporting cells, influencing cytokines important for cell growth. Kumar et al. [12] reported an incidence of hypertension of 5% in patients treated upfront with combination of ixazomib, lenalidomide, and dexamethasone, but the TOURMALINE MM1 study, investigating the safety and efficacy profile of ixazomib, did not find significant differences in the incidence of CVAE between the ixazomib and placebo arms [13]

3.6. Cardiotoxicity of Immune Checkpoint Inhibitors (ICI). Immune checkpoints have the role to prevent exaggerated immune response, while inhibition of them enhances immune activity, facilitating the antitumor immune response. They represent promising therapies in many refractory hematologic malignancies. Besides immune-related side effects, there are also cardiovascular adverse events described, like myocarditis, takotsubo syndrome, acute coronary syndrome, and pericardial disease [14].

4. Definition of Cardiac Dysfunction Secondary to Chemotherapy

Cancer therapy-related cardiac dysfunction is defined as a reduction of LVEF > 10% from baseline, with a LVEF lower than the normal limit. The cutoff for normality is considered 50%, but in patients treated with anthracyclines or trastuzumab, a LVEF in the low-normal range (50-55%) is associated with an increased risk of cardiotoxicity. Thus, the recommendation of the American Society of Echocardiography and the European Association of Cardiovascular Imaging is to consider 53% as the lower normal limit [1, 15, 16].

5. Evaluation of Cardiotoxicity Risk and Strategies of Prevention

In a large retrospective study including 820 cancer patients, 3.5% developed cardiac toxicity during the 10-year period, but there was no correlation between cardiac toxicity and traditional cardiovascular risk factors like age, sex, hypertension, diabetes, hyperlipidemia, obesity, and smoking. This raises the possibility of genetic predisposition for the development of cardiovascular toxicity [17].

Although there are no known predictive risk factors for the development of cardiotoxicity, a baseline risk assessment is mandatory in all patients before initiation of therapy, focusing on early, preclinical detection of cardiotoxicity. This would help to identify patients who could benefit from cardioprotective drugs and to adjust therapy before irreversible cardiac injury develops. Tests used to assess cardiac toxicity are cardiac imaging and biomarkers.

5.1. Cardiac Imaging for Early Detection of Cardiotoxicity. The goal of cardiac imaging is to assess cardiac structure and function and to identify early cardiac injury. This includes echocardiography, nuclear imaging, and magnetic resonance imaging (MRI).

Measurement of LVEF is a relatively insensitive tool for detection of early cardiotoxicity because important changes in LVEF occur only after a significant amount of myocardial damage is done and the compensatory mechanisms are overcome, but echocardiography is still widely used due to its availability and lack of radiation exposure. LVEF is routinely measured by echocardiography of multigated acquisition (MUGA). Although standard 2-dimensional (2D) echocardiographic assessment of LVEF has a higher interobserver and intraobserver variability than MUGA (8.8% vs. 6.8%), it offers additional information on valvular and diastolic function [18].

A disadvantage of 2D echocardiography is that the LVEF measurements depend on the quality of the images. The endocardial border has to be sufficiently visualised to track the end-systolic and end-diastolic volumes. The use of contrast agents can improve endocardial visualisation and reduce interobserver and intraobserver variability. Although several trials demonstrated the usefulness of contrast agents in the clinical practice, there are no clear indications of their use in the guidelines of the American Society of Echocardiography and the European Association of Echocardiography. Besides poor endocardial definition, other limitations of 2D echocardiography are ventricular foreshortening and the use of mathematical models and geometrical assumptions for calculating the LV volumes. Three-dimensional (3D) echocardiography can overcome these limitations, allowing

a more accurate measurement of LV volumes and ejection fraction. Other advantages of 3D echocardiography are reduced analysis time, higher reproducibility, and lower interobserver variability. LV volumes obtained by 3D echocardiography correlate more closely with those obtained by computed tomography and MRI [18].

Another more sensitive tool for detection of early cardiac dysfunction is diastolic parameters. A study on 20 breast cancer patients with normal systolic functions has demonstrated that 50% of the patients treated with anthracyclines had impaired early peak flow velocity to atrial flow velocity ratio, deceleration time, and isovolumetric relaxation time [19]. A prospective study on 26 patients treated with anthracycline demonstrated an association between early alterations of diastolic parameters and the development of left ventricular dysfunction. Despite these observations, larger studies are needed to confirm the role of diastolic measurements in detection of cardiotoxicity.

Exercise and pharmacologic stress testing could also detect early changes in the LV function. A study on 37 patients treated with anthracycline revealed that an abnormal LVEF at rest after 1 month had a sensitivity of 53% and a specificity of 75% for detecting the risk of developing cardiac failure [19]. The addition of exercise increased the sensitivity to 89% but decreased the specificity to 41%. Another study on 23 patients with acute lymphoblastic leukemia treated with anthracyclines demonstrated a normal EF at rest but a reduced LVEF during stress [19]. Also, a study made on 49 patients with breast cancer revealed a subtle alteration of myocardial contractile function in 17% of them during low-dose dobutamine [20].

Myocardial deformation (strain) and deformation rate (strain rate) have the advantage over LVEF measurement to offer a multidimensional evaluation of myocardial mechanics and to detect subtle wall motion abnormalities that do not decrease LVEF. Several studies have demonstrated that strain and strain rate are more sensitive measures than LVEF for early detection of LV dysfunction [21–23]. A study on women treated with trastuzumab for breast cancer revealed that 51% of the patients had reductions in 2D longitudinal strain values and 37% reduction in 2D radial strain. Another study on 16 breast cancer patients treated with liposomal doxorubicin showed no changes in LV dimensions, LVEF, and systolic myocardial velocity at the end of chemotherapy, while longitudinal and radial strain and strain rates were significantly changed [24]. Strain measurements can also identify long-term effects of chemotherapy. In a cohort of 56 late survivors of childhood cancer treated with anthracyclines, strain measurements detected subclinical cardiotoxicity; both radial and longitudinal myocardial strain measurements were reduced by 15%, while LVEF remained normal [22].

Isotopic ventriculography is not currently used for monitoring cardiotoxicity due to the risk of ionizing radiation.

Cardiac MRI (CMR) can assess cardiac structure and function, and it can also evaluate pericardium, characterize myocardial tissue, and assess for cardiac infiltrates. CMR is a noninvasive method that offers a comprehensive assessment of myocardial function and myocardial tissue characterization, including assessment of strain, edema, and fibrosis. CMR can be used for LV chamber size quantification and systolic function measurement, providing quantification of chamber size and LVEF which is free from geometric assumptions and independent of acoustic windows. CMR myocardial tagging is also a well-established technique for measuring myocardial strain and was first described by Zerhouni et al. in 1988 [25]. Drafts et al. studied CMR parameters on cancer patients receiving anthracyclines before and 1, 3, and 6 months after therapy. After 6 months, LVEF decreased from $58 \pm 1\%$ to $53 \pm 1\%$ ($p = 0.0002$) and midwall circumferential strain from -17.7 ± 0.4 to -15.1 ± 0.4 ($p = 0.0003$) without evidence of focal fibrosis as defined by late gadolinium enhancement (LGE) [26]. CMR imaging with LGE is the reference standard for the noninvasive detection of focal myocardial fibrosis. Another advantage of CMR for evaluation of potential cardiotoxicity is the use of noncontrast parametric mapping techniques such as native T1 and T2 mapping, which rely on the intrinsic magnetic relaxation properties of the myocardium [27]. Immune checkpoint inhibitors often cause myocarditis, sometimes with fulminant evolution, which can also be diagnosed by CMR. In conclusion, CMR is a useful supplemental modality to echocardiography when a more reliable EF measurement is needed as well as for better tissue characterization [28].

5.2. The Role of Biomarkers in Early Detection of Cardiotoxicity. The poor sensitivity and variable reproducibility of LVEF measurements for detecting early cardiomyopathy have led to development of cardiac biomarkers. They offer an alternative solution for the shortcomings of imaging. There is no radiation exposure, and they are easier to perform than imaging. Several cardiac biomarkers have been proposed, the most studied ones being troponin and natriuretic peptides, reflecting cardiomyocyte damage and elevation in left ventricular filling pressure and wall stress, respectively. Other biomarkers are markers of inflammation: C-reactive protein (CRP), interleukin-6 (IL-6), and myeloperoxidase; of endothelial dysfunction: plasminogen activator inhibitor (PAI), tissue-type plasminogen activator (t-PA), and soluble intercellular adhesion molecule; and of myocardial ischemia: fatty acid binding protein, glycogen phosphorylase BB, and neuregulin-1 [29].

(a) Troponins: cardiac troponins (cTn) are markers of myocardial damage and they are released in response to ischemia, inflammation, oxidative stress, or apoptosis. They are the best studied markers of anthracycline cardiotoxicity. Increased cTn1 is present in one-third of patients treated with anthracyclines, and the proportion of patients with elevated cTn1 increases with the cumulative dose of anthracyclines. Elevation of cTn1 occurs early, within 12 hours in 53% of the patients. Therefore, measurement of cTn1 in the first 24 hours after treatment can detect early cardiotoxicity. cTn1 elevation can also predict late cardiac toxicity [30]. The pattern of cTn1 elevation offers prognostic information; in a study of 703 patients, a persistent cTn1 elevation 1 month after stopping

anthracycline therapy was associated with higher incidence of cardiac events than in those with transient elevation [31]. Even before chemotherapy, in particular, patients with hematologic malignancies can have increased levels of cTn1, suggesting that the tumor itself can cause cardiac damage. cTn1 appears to have a higher predictive value than cTnT (troponin T), especially in leukemic patients [32]. Although troponins are sensitive and specific markers of cardiac injury, they can be elevated in other conditions too, like hypertensive emergency, renal failure, rhabdomyolysis, sepsis, and poor vascular health, thus limiting their use in predicting cardiotoxicity [33]

(b) Natriuretic peptides (B-type natriuretic peptide-BNP and its amino-terminal fragment-NT-pro-BNP) are markers of elevated left ventricular filling pressure and wall stress. Most of the studies have found a correlation between NT-pro-BNP elevation and cardiac dysfunction [29]. There is also a correlation between NT-pro-BNP and the cumulative anthracycline dose [34]. Patients with elevated NT-pro-BNP levels before chemotherapy had a higher risk of cardiotoxicity [35]. Similar to cTn1, elevation of BNP shortly after chemotherapy is a predictor for late cardiotoxicity. The pattern of elevation of BNP is also a prognostic factor; in a cohort of 52 patients treated with chemotherapy, persistently elevated NT-pro-BNP was strongly associated with development of cardiac dysfunction, compared to those with transient elevation, in whom no significant LVEF changes appeared during the 12-month follow-up [36]. A prospective study on 333 anthracycline-treated patients analyzed the predictive value of elevated BNP and LVEF obtained by MUGA for hospitalisation for congestive heart failure and mortality. This study found that both BNP and LVEF are independently predictive for congestive heart failure, but only BNP was associated with increased mortality. Future prospective trials are needed to standardize the use of BNP to diagnose patients with cardiac damage and to determine the optimal cutoff level and the timing for obtaining BNP samples. Also, future studies should focus on therapeutic decision-making according to BNP concentrations [37]. The use of natriuretic peptides for assessing cardiotoxicity has some limitations, evidence suggesting higher levels in the elderly and females, in case of renal failure, and the malignancy itself can increase BNP levels

(c) Markers of inflammation: studies have not demonstrated a direct correlation between inflammation markers like CRP, IL-6, and myeloperoxidase, but it can be assumed that changes in the antioxidant defence capacity may be associated with anthracycline-induced cardiotoxicity [29]. High-sensitivity CRP (hs-CRP) has been assessed for predicting cardiotoxicity in a study which included 49 women treated with trastuzumab. This trial showed a correlation between hs-CRP levels and the later onset of cardiomyopathy. Interestingly, hs-CRP levels appear to be higher in childhood cancer survivors, even if they were not exposed to cardiotoxic therapy, suggesting that hs-CRP is a marker of overall inflammation or tumor burden, in addition to chemotherapy effect [38]. Myeloperoxidase (MPO) is an enzyme produced by neutrophils and can lead to production of free radicals and to lipid peroxidation. One study showed that MPO levels after anthracycline administration correlated with the development of cardiotoxicity [39]

(d) Markers of endothelial dysfunction: activation of endothelium can lead to vascular dysfunction and accelerated atherosclerosis. A study on 90 patients with testicular cancer demonstrated higher levels of fibrinogen, CRP, von Willebrand factor, PAI-1, and t-PA in patients treated with chemotherapy, compared to those treated only with surgery. Those with higher PAI-1 levels had higher triglyceride levels, body mass index, and blood pressure and decreased carotid artery distensibility compared to controls. Increased levels of endothelial dysfunction markers suggest an increased risk of accelerated atherosclerosis [29, 30]

(e) Markers of myocardial ischemia: studies have demonstrated increased levels of fatty acid-binding protein (FABP) and glycogen phosphorylase-binding protein (GPBB) after chemotherapy, suggesting they could be a potential marker of cardiotoxicity [29]. In a study of patients treated with high-dose chemotherapy followed by stem cell transplantation, a group of patients with positive signal for GPBB was identified, without elevations of cTn or BNP; however it is difficult to demonstrate that GPBB is a more sensitive predictor for myocardial damage in the absence of long follow-up. Future larger trials are needed to assess the potential utility of GPBB [40]

(f) Neuregulin-1 (NRG-1) is a growth factor released by endothelial cells that bind to receptors on myocytes and stimulates cell growth, survival, and repair. A prospective study on 78 women treated with anthracycline for breast cancer showed a significant decrease of NRG-1 levels, suggesting the loss of this cardioprotective growth factor [29]

(g) Circulating microRNAs are short noncoding RNAs that play an important role in maintaining homeostasis, being implicated in regulation of oxidative stress response and cellular injury. Preclinical studies demonstrated increased levels of microRNAs (miR-146a) after doxorubicin administration [41]. Some microRNAs have been linked to specific cardiovascular diseases. The most investigated cardiac microRNAs are miR-1, miR-133, miR-208, and miR-499. A study involving 33 children demonstrated elevated miR-29b and miR-499 after anthracycline therapy,

and the degree of elevation correlated with the anthracycline dose and troponin rise [42]. Another study involving breast cancer patients treated with doxorubicin revealed an increase in miR-1 which was strongly associated with LVEF reduction and was superior to troponin level in predicting cardiotoxicity [43]. MicroRNA level could be a marker specific for inflammatory or injury-mediated cardiotoxicity and heart failure; however, future studies are necessary for assessing the role of mIR-146a in chemotherapy-induced cardiotoxicity [41]

(h) Other novel emerging biomarkers are ST2, galactin-3, and growth differentiation factor 15 (GDF-15). There are only few studies investigating the potential role of these novel biomarkers in detecting chemotherapy-induced cardiotoxicity; some of them showed no significant association with cardiotoxicity; however, GDF-15 is an indicator of inflammation and oxidative stress and a promising parameter for detecting late cardiotoxicity. Future larger studies are needed to assess the role of these novel biomarkers [44]

6. Strategies to Prevent Cardiotoxicity

In order to reduce cardiotoxicity risk in cancer patients, several measures should be taken, including encouraging of a healthy lifestyle (regular exercise, healthy diet, and cessation of smoking) and identification and treatment of cardiovascular risk factors like dyslipidemia, increased glycated hemoglobin, and hypertension.

Other strategies to reduce cardiotoxicity include limiting the cumulative dose of cardiotoxic drugs and using less cardiotoxic regimens (liposomal anthracyclines).

The use of cardioprotective drugs is also a method to prevent/reduce cardiotoxicity. Cardioprotective agents used for prevention are as follows:

(i) Dexrazoxane

(ii) Beta-blockers (carvedilol, nebivolol) that prevent LVEF reduction and decrease the incidence of heart failure

(iii) Angiotensin-converting enzyme inhibitors (enalapril) that prevent LVEF deterioration during anthracycline therapy

(iv) Combination therapies: in a paper published in 2016, the European Society of Cardiology recommended the use of cardioprotective drugs, like angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers in association with beta-blockers. The OVERCOME trial demonstrated that patients who received enalapril and carvedilol had no reduction in LVEF at 6 months, compared to those who did not receive these drugs

(v) Statins that reduce cellular damage and heart failure risk during anthracycline treatment [1–3]

7. Monitoring Treatment-Related Cardiotoxicity

Initial evaluation of patients includes medical history and physical examination, electrocardiography, structural and functional evaluation (by echocardiography and biomarkers), risk stratification, and treatment of cardiovascular risk factors.

Monitoring during treatment should include transthoracic echocardiography at baseline and at the end of therapy (in case of TKIs, also every 3 months) and biomarkers (troponin +/- pro-BNP) before each cycle of therapy. Patients who present decreased LVEF or increased biomarkers at baseline or during therapy need cardiologic consultation and more frequent monitoring and, in selected cases, even adjustment of treatment [1].

8. Management of Therapy-Related Cardiotoxicity

(i) Heart failure (HF): asymptomatic patients with reduced LVEF need beta-blocker and ACE inhibitors to prevent clinical HF. They can be identified by elevated troponins or a decrease of global longitudinal strain > 15%. Chemotherapy withdrawal decisions should be made weighing the HF risk against the risk of cancer progression or relapse

(ii) Hypertension is a common comorbidity in cancer patients and can be also caused by treatment, especially by VEGF (vascular endothelial growth factor) inhibitors. Monitoring blood pressure during therapy is important in order to prevent other complications, the target blood pressure being <140/90 mmHg in those with uncomplicated hypertension and <140/85 mmHg in those with diabetes or renal failure. The drugs of choice are ACE inhibitors, angiotensin receptor blockers, and beta-blockers. In case of poor control, amlodipine or aldosterone inhibitors could be added. Negative inotropes should be avoided due to the risk of HF

(iii) Arrhythmias: both tachyarrhythmias and bradyarrhythmias can occur in chemotherapy patients and treatment includes rate control, sometimes anticoagulants and pacemaker implantation in case of symptomatic bradycardias

(iv) Ischemic heart disease (IHD): patients treated with drugs associated with high risk of IHD (etoposide, bleomycin, vinblastine, etc.) should be closely monitored, and nitroglycerine or calcium antagonist should be given in case of angina

(v) Myocarditis and pericarditis are rare complications of chemotherapy, and their treatment follows the general recommendations

(vi) Venous thromboembolic disease (VTD) is a common complication in cancer patients, caused by

the malignancy itself but also favored by some treatments, like IMIDs, TKIs, and, in many cases, prophylactic treatment is necessary

(vii) Pulmonary hypertension is seen mostly in patients treated with Dasatinib or Cyclophosphamide; therefore, these patients should be closely monitored with echocardiography

(viii) Peripheral vascular disease: administration of nilotinib and ponatinib can be associated with arterial thromboembolism and early atherosclerosis, so correction of cardiovascular risk factors is important [1]

9. Long-Term Monitoring of Chemotherapy-Related Cardiotoxicity

Long-term follow-up is indicated for those patients who received a cumulative anthracycline dose of >250 mg/m^2 or>35 Gy chest radiotherapy or a combination of anthracycline > 100 mg/m^2 and radiotherapy > 15 Gy. Echocardiography is the method of choice for follow-up and should be performed 2 years after treatment and then every 5 years [1].

10. Guidelines for Management of Chemotherapy-Induced Cardiotoxicity

There are several guidelines regarding cardiotoxicity, proposed by the European and American cardiology societies. A cardio-oncology expert panel from the French Working Group of Cardio-Oncology analyzed the most recent American and European guidelines (American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO), and European Society of Cardiology (ESC)) and proposed decision algorithms easy to use by clinicians in their daily practice.

All of the guidelines emphasize the need to identify patients with an increased risk of developing cardiovascular toxicity. Differences exist, but all of the definitions include patients with previous cardiovascular diseases, high-dose anthracycline, and combination therapy (Table 1).

The working group proposed the concept of the "cardio-oncological evaluation," a global and standardized cardiovascular assessment strategy of patients with cancer, including risk factor assessment, ECG, biomarkers, and imaging evaluation (Table 2).

The working group also proposed an algorithm for management of cardiotoxicity.

(A) Management of overt treatment-related left ventricular systolic dysfunction (drop of LVEF with 10% to a value < 50% or a drop of 20%)

(1) Asymptomatic patient: cardio-oncological evaluation and initiation of angiotensin-converting enzyme inhibitors (ACEI) and beta-blockers (BB)

Table 1: Patients with high risk of cardiotoxicity.

(i) High-dose anthracycline (e.g., doxorubicin ≥ 250 mg/m^2 and epirubicin ≥ 600 mg/m^2)
(ii) High-dose radiotherapy (≥30 Gy) if the heart is in the treatment field
(iii) Lower-dose anthracycline (e.g., doxorubicin < 250 mg/m^2 and epirubicin < 600 mg/m^2) or HER inhibitors or VEGF inhibitors or proteasome inhibitors of Bcr-Abl tyrosine kinase inhibitors and presence of any of the following factors:
(a) Age ≥ 60 years
(b) Lower-dose radiotherapy (<30 Gy) where the heart is in the radiation field
(c) ≥2 risk factors, including smoking, hypertension, diabetes mellitus, dyslipidemia, chronic renal insufficiency, and obesity
(iv) Previous heart disease
(v) Elevated cardiac biomarkers (pro-BNP, NT-pro-BNP, and troponin) before initiation of anticancer therapy

(i) LVEF > 40%: in case of chemotherapy without anthracycline, continue the same treatment as long as the patient is asymptomatic + physical examination, transthoracic echocardiography, BNP, or NT-pro-BNP at 3 weeks then every 3 months. In case of anthracycline therapy, the same strategy as in those with LVEF < 40%

(ii) LVEF < 40%: withhold therapy + physical examination, transthoracic echocardiography, BNP, or NT-pro-BNP at 3 weeks then every 3 months. In case of increasing LVEF, discuss resuming therapy

(2) Symptomatic patient (heart failure): cardio-oncological evaluation and initiation of angiotensin-converting enzyme inhibitors and beta-blockers, holding the involved cancer treatment and close cardio-oncological monitoring. In case of remission of symptoms (NYHA I), it can be discussed to restart therapy. In case of persistency of symptoms (NYHA II-IV), permanently stop the involved treatment

(B) Management of early cancer treatment-related myocardial toxicity: troponin rise > 99% of the upper reference limit and/or absolute global longitudinal strain (GLS) drop > 5% or ΔGLS > 12%

(1) Troponin rise AND GLS drop > 5% or ΔGLS > 12%: cardio-oncological evaluation before the next administration and at 3 weeks initiate ACEI and/or BB. Cardio-oncological evaluation at 3 weeks and every 3 months unless symptoms develop. Continue

Table 2: Cardiovascular assessment included in the "cardio-oncological evaluation".

(i) Clinical consultation (including blood pressure measurement)
(ii) ECG
(iii) Blood glucose, lipid profile, and glomerular filtration rate calculation
(iv) Cardiovascular global risk assessment using guidelines
(v) Transthoracic echocardiogram (TTE), including measurements of LVEF (ideally 3D but at least 2D) and GLS; in the absence of GLS quantification of LV longitudinal function, use mitral annular displacement by M-mode echocardiography and/or peak systolic velocity of the mitral annulus by pulsed-wave DTI
(vi) LV contrast agents could be potentially useful in 2D echocardiography
(vii) Cardiac magnetic resonance is recommended if the quality of TTE is suboptimal
(viii) Use the same imaging modality for monitoring
(ix) Actively manage modifiable cardiovascular risk factors and diseases
(x) Encourage exercise on a regular basis and healthy dietary habits

the same treatment as long as no LVEF drop or symptoms

(2) Troponin rise OR GLS drop > 5% or ΔGLS > 12%: cardio-oncological evaluation before the next administration and at 3 weeks discuss ACEI and/or BB. Cardio-oncological evaluation at 3 weeks and every 3 months unless symptoms develop. Continue the same treatment as long as no LVEF drop or symptoms [45]

11. Conclusions

Recent discoveries in oncology significantly improved overall survival of cancer patients, but they have also led to more complications of treatment. Some of these treatment-related complications are transient, but unfortunately, many have permanent impact on the quality of life and survival. Besides secondary malignancies, a life-threatening complication of cancer treatment is cardiac toxicity; therefore, a multidisciplinary approach is mandatory, to find a balance between the need for cancer cure and potential cardiotoxicity. As in other diseases, prevention is better than cure, hence the necessity to find methods with high sensitivity and sensibility to detect early, subclinical changes and allow prompt intervention to prevent further damages. Since imagistic methods are not able to detect early structural changes, cardiac biomarkers are promising parameters for early intervention. Although cardiac biomarkers, like troponin and NT-pro-BNP, have demonstrated their superiority over cardiac imaging, they are not routinely included in initial assessment and monitoring. A joint effort of oncologists and cardiologists is needed to elaborate guidelines for diagnosis and management of chemotherapy-related cardiotoxicity.

Data Availability

The data supporting this systematic review are from previously reported studies and datasets, which have been cited. The processed data are available from the corresponding author upon request.

Conflicts of Interest

We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work; there is no professional or other personal interest of any nature or kind in any product, service, and a company that could be construed as influencing the position presented in, or the review of, the manuscript entitled.

Authors' Contributions

All authors contributed equally to this manuscript.

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Review Article

ECG Markers of Cardiovascular Toxicity in Adult and Pediatric Cancer Treatment

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When a cardiologist is asked to evaluate the cardiac toxic effects of chemotherapy, he/she can use several tools: ECG, echocardiography, coronary angiography, ventriculography, and cardiac MRI. Of all these, the fastest and easiest to use is the ECG, which can provide information on the occurrence of cardiac toxic effects and can show early signs of subclinical cardiac damage. These warning signs are the most desired to be recognized by the cardiologist, because the dose of chemotherapeutics can be adjusted so that the clinical side effects do not occur, or the therapy can be stopped in time, before irreversible side effects. This review addresses the problem of early detection of cardiotoxicity in adult and pediatric cancer treatment, by using simple ECG recordings.

1. Introduction

In the last twenty years, the survival and life expectancy of adults and children with cancer have risen significantly, mainly due to the new chemotherapy. However, chemotherapeutic agents have secondary and adverse effects, some of them dreadful. Their early recognition can prevent the development of associated sometimes fatal pathologies. Monitoring

the cardiac side effects of chemotherapy is feasible generally using echocardiography, radionuclide ventriculography, dosing cardiac biomarkers [1] such as BNP and NT-proBNP [2], and ECG. Sometimes, these techniques may identify subclinical heart damage [3] before the clinical manifestation by heart failure, chronic coronary syndrome, or myocardial infarction. Therefore, an attempt was made to discover early markers of toxicity, and the purpose of this review is to present published data on ECG changes as markers of cardiac toxicity caused by chemotherapeutics. The 12-lead surface ECG is a simple examination that is performed quickly in about 3 minutes and can provide information on cardiotoxicity, which is mainly manifested by ischemic changes or by arrhythmias. Of course, there are more subtle changes, which can precede the installation of arrhythmias: for example, bifid and broad P wave lasting more than 120 ms that precedes the installation of atrial fibrillation or the prolonged QT interval > 500 ms that precedes in some cases the installation of torsade de pointes. Sometimes, the presence of multiple atrial ectopic beats may require stopping chemotherapy in order to prevent atrial fibrillation; the presence of numerous PVCs with multiple morphologies may require discontinuation of chemotherapy due to an increased risk of malignant ventricular arrhythmias such as polymorphic ventricular tachycardia or ventricular fibrillation. These ECG markers are easily recognizable by the clinical cardiologist or interventional arrhythmologist but are more challenging for an oncologist or general practitioner. The ECG does involve not only 12-lead recording but also derivatives such as recording with a monitor during hospitalization, single-lead or two-lead monitoring at home with a portable monitor (Omron, Heal Force Print 180 D, 180B), and monitoring by Apple devices, smartwatch, smartphones, Holter ECG/24 hours, exercise stress test, or electrophysiological study [4]. These are derivatives of the 12-lead ECG, and we will not refer to them in this review. The electrocardiographic changes given by chemotherapy can be transient, and therefore, other methods than the standard ECG are used to detect them. Generally, before starting chemotherapy, it is suitable for the patient to have a baseline ECG recording so that later, after starting the treatment, the measurements may be compared with the initial recording.

2. Arrhythmogenic Mechanisms of Chemotherapy

There are several mechanisms by which chemotherapy can become proarrhythmogenic (Table 1):

(1) By the effect of direct damage to the myocardial cell with the release of natriuretic peptides BNP, NT-proBNP, and troponin, with the development of ischemic or nonischemic dilated cardiomyopathy, increased left ventricular filling pressures, and subsequently left atrial and fibrillation

(2) Coronary spasm with the induction of myocardial ischemia or a direct effect of the chemotherapeutic on coronary vascularization with secondary ischemia, with or without myocardial necrosis and arrhythmogenesis by the formation of abnormal reentry circuits or abnormal depolarizations

(3) Action at the level of ion channels with impaired ventricular depolarization or repolarization, prolongation of the QT interval, and induction of polymorphic ventricular tachycardia (torsade de pointes)

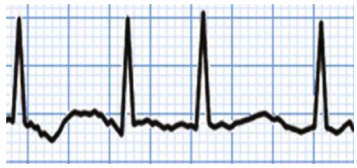
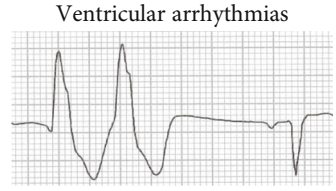
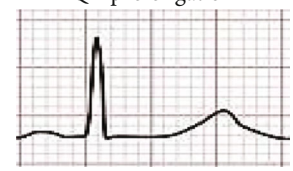
(4) Direct action on the conduction system: sinus node, atrioventricular node, His, left or right branch, respectively, and Purkinje network

One of the most common side effects of chemotherapy that can be detected on the ECG in 12 leads is sinus bradycardia. Taxanes and angiogenesis inhibitors (thalidomide) can cause sinus bradycardia, most likely through a direct action on the sinus node. Nevertheless, taxanes can have effects at other levels of the atrioventricular conduction system. Thus, paclitaxel can affect the infrahisian conduction system (after the bifurcation of the His) and lead to the appearance of the right or left branch block. If the lesion is located at the suprahisan level, atrioventricular blocks of varying degrees, from 1 to 3, may occur. The conduction disorders generally occur within 4 hours of initiating the paclitaxel infusion and disappear after stopping the chemotherapeutic, usually within the first 48 hours [5]. The mechanism by which paclitaxel affects the conduction system is either directly by affecting the sinus node, atrioventricular node, and His-Purkinje system or indirectly by affecting the parasympathetic nervous system, which induces bradycardia or conduction disorders. Thalidomide-induced sinus bradycardia is also explained by the action on the sympathetic nervous system [6] and also the induction of a manifest clinical or subclinical hypothyroidism which is in turn associated with sinus bradycardia by intrinsic remodeling of the sinus node [7]. On the other hand, thalidomide has also been implicated in the development of rapid ventricular arrhythmias, especially ventricular tachycardia [8].

Another mechanism promoting cardiac arrhythmias is through myocardial ischemia [9] or even necrosis if myocardial ischemia persists for a long time. Thus, alkylating agents cisplatin, cyclophosphamide [10], ifosfamide, and melphalan may promote coronary vasospasm, cardiomyocyte damage, and endothelial damage. Up to 10% of cisplatin users develop atrial and ventricular arrhythmias within the first 24 hours-3 days of initiating treatment, with the disappearance of these side effects within approximately 1 week. Melphalan has also been implicated in the genesis of episodes of atrial fibrillation or atrial flutter [11].

Anthracyclines cause atrial and ventricular arrhythmias by inducing structural cardiomyopathy associated with decreased left ventricular systolic function with altered ejection fraction. This decrease in ejection fraction leads to increased left ventricular end-diastolic pressure and increased left intra-atrial pressure and favours atrial arrhythmias such as extrasystoles, atrial tachycardia, or atrial fibrillation. On the other hand, the marked decrease of the ejection fraction may favour ventricular arrhythmias: premature ventricular contractions, ventricular tachycardia, and ventricular fibrillation.

Table 1: Proarrhythmic risk of chemotherapy: atrial, ventricular, and QT prolongation.

	Atrial arrhythmias	Ventricular arrhythmias	QT prolongation
			
Anthracyclines	Atrial fibrillation with doxorubicin	Small case series	Rare cases
Antimetabolites	Small case series	Small case series	Rare cases
Cyclophosphamide	Rare cases	Never	Never
Melphalan	Atrial fibrillation and flutter	Never	Never
Trastuzumab	Rare cases	Rare cases	Never
Tyrosine kinase inhibitors	Atrial fibrillation with ibrutinib	Large studies: PVCs and VT	Small studies QT prolongation of 5-15 ms No QT prolongation with ibrutinib
Antimicrotubule agents	Rare cases	Small case series	Never
Arsenic trioxide	Rare cases	Small studies	Small studies showed QT prolongation > 450 ms and even >450 ms
Thalidomide	Atrial fibrillation	Small case series	Never
Histone deacetylase inhibitors	Never	Large studies: PVCs and VT	Small studies Therefore contraindicated if QT > 450 ms
IL-2	Small studies	Small studies	Never
Amsacrine	Small studies	Small case series	Rare cases, associated with hypokalemia

Large studies demonstrated atrial arrhythmias for melphalan, ventricular arrhythmias for tyrosine kinase inhibitors and histone deacetylase inhibitors, and QT prolongation for tyrosine kinase inhibitors, histone deacetylase inhibitors, and arsenic trioxide.

5-Fluorouracil validates its arrhythmogenic effects through coronary vasospasm and the myocardial ischemia it induces. Like 5-FU, interleukin-2 promotes arrhythmias by inducing vasospasm with consequent prolonged myocardial ischemia or myocardial inflammation (myocarditis) [12].

3. ECG Modifications and Arrhythmias Induced by Different Chemotherapeutics

3.1. Anthracyclines. Anthracyclines are currently used to treat leukemias, lymphomas, breast cancer, and solid pediatric tumors. Generation I anthracyclines (daunorubicin and doxorubicin) have as a side effect the irreversible development of nonischemic dilated cardiomyopathy, and their effects are cumulated with increasing doses and duration of use (an incidence of 5-8% is observed at a cumulative dose of 450 mg/m^2) [13].

A study by Kilickap's team that involved Holter EKG monitoring for 48 hours of patients immediately after doxorubicin infusion showed a paroxysmal atrial fibrillation rate of 10.3% [14]. However, when ECG monitoring was performed at each visit for the continuation of chemotherapy, a 6% incidence of this arrhythmia was recorded [15]. The highest detection rate (56.6%) was objectified by interrogating the implantable defibrillator in patients with cardiac dysfunction associated with chemotherapy [16]. The same study shows that the incidence of nonsustained ventricular tachycardia can reach up to 73.9% of cases, similar to those in the control group, of patients with nonischemic cardiomyopathy, not related to anthracyclines (was not significantly different from non-anthracycline-related cardiomyopathy and dilated cardiomyopathy or ischemic heart disease) [16]. However, premature ventricular contractions remain the most common form of anthracycline-induced ventricular arrhythmia (the number of bigeminal ventricular extrasystoles increased significantly, $p < 0.05$) [17].

A study analyzing the effects of epirubicin on QTc interval dispersion (defined as the difference between the maximum and minimum QT intervals on the recorded electrocardiogram) showed an increase in this parameter in all patients included in the research. When dexrazoxane was administered in addition to epirubicin, the dispersion of the QT interval decreased statistically ($p < 0.05$) compared to the group without dexrazoxane [18].

3.2. Alkylating Antineoplastic Agents. Alkylating agents are frequently used before stem or bone marrow transplantation. Several factors increase the risk of developing this melphalan-induced arrhythmia, including advanced age (over 63 years: risk ratio: 4.8 (95% confidence interval (CI) 3.2-7.6), $p < 0.001$), dilated left atrium over 33 cc/m^2 (risk ratio: 2 (95% CI 1.3-3.1), $p < 0.001$), left ventricular systolic dysfunction ($p < 0.001$), and even cardiac amyloidosis (this was not significant, $p = 0.08$) [19, 20]. Besides, when a supraventricular arrhythmia occurs after hematopoietic stem cell transplantation, the prognosis of these patients worsens as observed in a study conducted by Tonorezos et al. on a group of 1177 patients. Of these, those with atrial fibrillation or flutter had

a higher risk of in-hospital death (28% vs. 3%, $p < 0.001$) and also one year after the intervention (41% vs. 15%; $p < 0.001$). Practically, the existence of arrhythmias in post-stem cell transplant patients has been an independent predictor of mortality with a greater risk for death within a year of transplant (odds ratio 3.5 (95% CI 2.1-5.9; $p < 0.001$)) [21].

Busulfan is another chemotherapeutic belonging to the alkylating agent class. The incidence of developing atrial fibrillation was up to 6.4% when used in combination with cyclophosphamide [22].

In conclusion, during treatment with alkylating agents, patients should be monitored for atrial fibrillation with melphalan and busulfan and also for the development of structural abnormalities that may be responsible for ventricular arrhythmias with cyclophosphamide and ifosfamide.

3.3. Anti-HER2 Agents. An analysis that included over 8000 patients treated with trastuzumab reported an incidence of atrial fibrillation of 1.2% after trastuzumab use (95% CI 0.56-2.68) [23]. On the other hand, a study published in 2015 by Pivot and colleagues compared the cardiac toxicity generated by trastuzumab after 6 months and 12 months of adjuvant treatment, respectively. Of the 3380 enrolled patients, only 0.65% had NYHA III/IV heart failure classes in the one-year treatment arm and 0.53% in the six-month treatment arm, with no statistically significant difference between the two groups. For NYHA I/II heart failure classes, the number of cases was significantly higher in the one-year treatment group (5.9%) than in the group receiving 6 months of treatment (3.4%) [24]. When trastuzumab was used after a "dose-dense" (accelerated) regimen of anthracyclines and taxanes, the enrolled patients showed a significant decrease in LVEF in a tiny percentage (1%) [25].

The use of trastuzumab with paclitaxel after an anthracycline and cyclophosphamide induction regimen resulted in symptomatic heart failure in 4% of patients enrolled in the study (95% CI 0.5-13.2), and in 21% of them, a decrease in LVEF below 50% was noticed (95% CI 11.1-34.7) [26].

Another study that evaluated the safety of administration of trastuzumab in the elderly found that of the 22 patients, only 2 had a 10% asymptomatic decrease in LVEF [27].

More extensive studies of approximately 45,000 women with a mean age of 76.2 years showed that the 3-year incidence of cardiomyopathy or heart failure of any grade was 32.1% in the trastuzumab-only group and 41.9% in patients who also received anthracyclines compared with no adjuvant therapy (18.1%, $p < 0.001$) [28].

Trastuzumab-emtansine (T-DM1), a combination used in the second line of treatment after trastuzumab, did not cause any significant cardiovascular events (including symptomatic heart failure) in the 153 patients evaluated in Krop et al.'s study [29].

Lapatinib is a safer product than trastuzumab in that it rarely induces left ventricular dysfunction and arrhythmias [30].

3.4. Tyrosine Kinase Inhibitors. These products do not induce structural abnormalities of the myocardium but may prolong the QT interval and induce ventricular arrhythmias such as torsade de pointes.

Ibrutinib is a Bruton tyrosine kinase inhibitor used in B-line haematological malignancies such as chronic lymphocytic leukemia and mantle cell lymphoma. A study conducted by Yun et al., published in 2017, shows an incidence of atrial fibrillation/flutter of 8.18% in patients treated with ibrutinib compared to placebo (8.18% vs. 0.93%, RR = 8.81, 95% CI 2.70-28.75, $p < 0.001$). It should be remembered that the risk of arrhythmia is proportional to the dose and time of treatment [31]. According to the HELIOS phase 3 trial published in 2018 in the *Leukemia* journal, the rate of occurrence of atrial fibrillation/flutter as an adverse event was reported at 4.9% [32]. Another study, published in the *NEJM*, showed similar incidences of atrial fibrillation of 6%. In 25% of the patients, it was necessary to stop the treatment, but for the rest, no intervention was needed [33]. Although ibrutinib carries a relatively high risk of atrial fibrillation, it also acts as an antiplatelet agent, associated with an increased risk of bleeding. Therefore, the use of antivitamin K in this category of patients has been discouraged. It seems that the new oral anticoagulants such as dabigatran, rivaroxaban, or apixaban have a higher safety profile [34].

Regarding Bruton tyrosine kinase inhibitors inducing ventricular arrhythmias, there is a reported incidence of 678 events/100,000 patients. Surprisingly, ibrutinib does not prolong the QTc interval; it even shortens it, although it does induce a risk of ventricular tachycardia [35].

3.5. Antimicrotubule Agents. In a study conducted by Rowinsky et al., 2 of the 140 patients treated with paclitaxel had a high-grade atrioventricular block and therefore required the implantation of a pacemaker. However, EKG monitoring of patients during injection is not indicated [36].

3.6. Immunomodulating Agents. Thalidomide is an agent used in the treatment of multiple myeloma that can cause bradyarrhythmias, including different types of atrioventricular block, both alone and in combination with other chemotherapeutics. Sinus bradycardia has been reported in 26% up to 53% of patients and most often resolves within 12-21 days of discontinuation of treatment [7].

Thalidomide was also associated with atrial fibrillation, with an incidence of 4.7% versus 3.4% in the placebo-treated arm. Therefore, cardiac monitoring is recommended in all patients treated with this immunomodulator [37].

Lenalidomide is another immunomodulator used in both multiple myeloma and myelodysplastic syndrome. It can induce supraventricular arrhythmias with an incidence ranging from 4.6 to 7% when used in combination with dexamethasone [38].

3.7. Amsacrine. This substance is used for the treatment of acute myeloid leukemia and electrophysiologically acts similar to anthracyclines. It can cause atrial and ventricular arrhythmias, respectively, and QT prolongation. However, proarrhythmic effects are rare and were reported in 0.7% in a study of 5340 patients [39]. The administration of amsacrine

is prone to hydroelectrolytic disturbances which may eventually lead to arrhythmias. Therefore, the use of this chemotherapeutic requires strict monitoring of the electrolytes (especially the level of potassium) to be administered safely, even in patients with left ventricular dysfunction [40].

3.8. Interleukin 2 (IL-2). The mechanism by which IL-2 induces cardiac arrhythmias is the increase of capillary permeability with tissue extravasation and hypotension and tachycardia. If those modifications occur in a structurally normal heart, they are not arrhythmogenic, but when they occur in an ischemic heart, they can produce atrial and ventricular arrhythmias. Another speculated mechanism is the action that different vasopressors have on the electrical system of the heart. Ventricular arrhythmias are also possible, but the frequency of life-threatening ventricular tachycardias is low, between 0.4 and 1.1% [41].

3.9. Trisenox (Arsenic Trioxide). Arsenic trioxide inhibits fast and slow potassium channels and activates ATP-dependent potassium channels. This is the electrophysiological mechanism underlying QT prolongation with a high risk of torsade de pointes. Approximately 38% of patients who are treated with arsenic trioxide develop QT prolongation > 450 ms and 27% > 500 ms [42]. The degree of QT prolongation was higher in male patients during the first cycle of treatment and also in patients with hypokalemia regardless of gender. Corrected QT intervals in these patients normalized up to the second cycle of chemotherapy, so it was considered that arsenic trioxide did not cause a permanent prolongation of the QTc interval [42]. Because life-threatening arrhythmias are rarely associated with arsenic trioxide, caution is advised in the use of QTc with the Bazett formula since the risk of cardiac toxicity may sometimes be overestimated, and therefore, cancer treatment may be unnecessarily discontinued. In these situations, alternative correction formulas are recommended [43]. Fortunately, the doses used in practice at this time are optimized so that ventricular arrhythmias occur with a fair frequency, but it is still necessary to monitor electrolytes and ECG in those patients, both before and during treatment [44].

3.10. Histone Deacetylase Inhibitors. These products, which are used to treat cutaneous T-cell lymphoma and multiple myeloma, can prolong the QT interval, and there have been reported cases of sudden death after starting treatment. For these reasons, they are contraindicated in the case of a QT interval over 450 ms. The underlying mechanism of arrhythmogenesis is not fully understood. However, it is currently accepted that these inhibitors interact with potassium hERG channels [45].

3.11. Antimetabolites. The most common side effects with 5-fluorouracil and capecitabine are chest pain, with or without EKG signs of ischemia. The mechanism of action is a coronary spasm. A spasm was demonstrated by reproduction in the radial artery after administration of 5-fluorouracil. The use of calcium channel blockers and long-acting nitrates has been proposed to counteract the vasospastic effects of antimetabolites [46].

4. Arrhythmias Determined by Long QT Interval

One of the most straightforward cardiotoxicity markers that can be measured on the surface ECG is the QT interval (Figure 1), an easy to measure, standardized interval, the most used method being the tangent method in derivation II or V5. Because ECG paper is often marked with lines or squares delimiting 40 ms, the measurement is easy considering the number of squares found along the length of the QRS complex and the T-wave. This interval represents depolarization along with ventricular repolarization. The QT interval measurement must not include the U-wave unless there is an evident fusion between T and U.

This QT interval is vital in arrhythmogenesis because when prolonged, it can be associated with polymorphic ventricular tachycardia, in this case called torsade de pointes. Not all polymorphic tachycardia is torsade de pointes but only that which is accompanied by an extended QT interval. In other cases, the term "torsade-like" can be used.

Due to the fact that the QT interval can be longer in the case of bradycardia and shorter in the case of tachycardia, there are mathematical formulas for correcting the QT interval depending on the frequency: Bazett, Fridericia, Framingham, and Hodges. It is considered that a corrected QT interval < 450 ms in men and <460 ms in women is normal. When the QT interval is >500 ms, the risk for torsade de pointes is high. Intervals between 450 and 500 ms considered the "grey area" should be monitored by serial recordings, and serum electrolytes should be checked for hypokalemia or hypomagnesaemia.

The 450 ms limit of the QT interval is considered too restrictive in cancer patients because if this limit was to apply, then over 10% of patients receiving chemotherapy would have to give up perhaps life-saving therapy [47]. On the other hand, in oncology patients, there have been found variations of the QT interval up to 60 ms within 24 hours. Thus, in cancer patients, a prolonged QT interval > 480 ms or an increase of >100 ms after the initiation of chemotherapy is considered significant [48, 49].

Cancer patients who are treated with antiarrhythmic medication for heart disease are at risk of developing drug interactions with the possibility of prolonging the QT interval. Class IA (quinidine and procainamide) and class III antiarrhythmics (amiodarone and sotalol) prolong the QT interval by their particular mechanism of action on ion channels. On the other hand, antiemetic drugs such as ondansetron and droperidol also prolong the QT interval. Among analgesics, methadone, an opioid derivative, also prolongs the QT interval (+14.1 msec, $p < 0.001$) [50]. Commonly used antineoplastic medication may also have the effect of prolonging the QT interval: tyrosine kinase inhibitors (rituximab, dasatinib, lapatinib, nilotinib, and sorafenib), anthracyclines (doxorubicin and daunorubicin), and antimetabolites (capecitabine, panobinostat, romidepsin, and vorinostat). These associations with antiarrhythmics should be avoided to prevent malignant ventricular arrhythmias such as torsade de pointes [51].

Arsenic trioxide is known to prolong the QT interval, which is why therapy should be stopped if the interval is

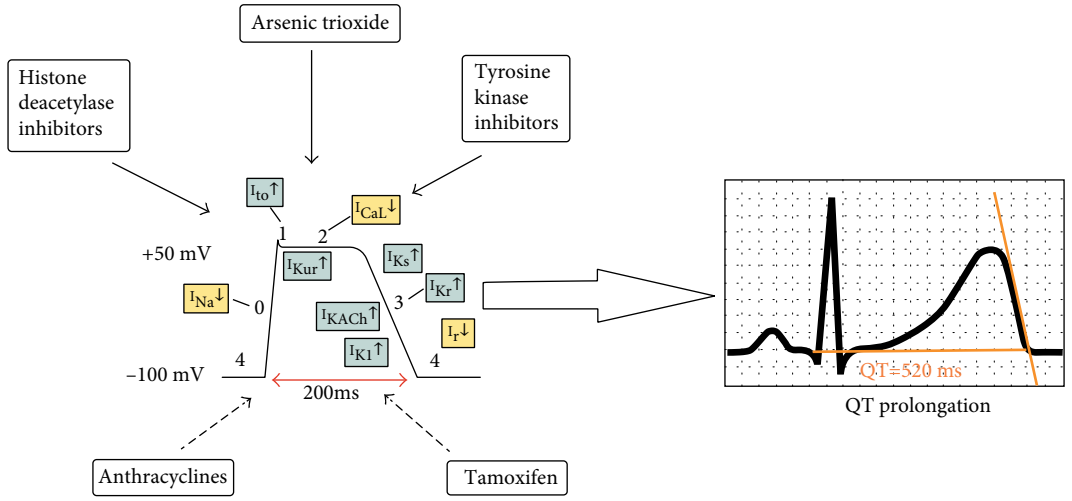


Figure 1: Chemotherapy that induces QT prolongation. Different agents act on different or more ionic channels prolonging ventricular depolarization and depolarization. A QT prolongation of >500 ms is considered dangerous and should lead to treatment cease.

prolonged >500 ms. When the interval decreases to 460 ms, the treatment can be resumed. Shen et al. [52], Niu et al. [53], and Unnikrishnan et al. [54] have published case reports of torsade de pointes in patients being treated with arsenic trioxide. However, there is also stronger evidence than isolated published cases. Thus, Ohnishi et al. [55] reported 8 cases of QT prolongation after arsenic trioxide infusion, but none of the 8 patients showed torsade de pointes. The most extensive patient studies of arsenic trioxide included approximately 100 patients. Thus, the study of Barbey et al. [42] on 99 patients observed QT prolongation over 500 ms in 26% of individuals. Only one of these patients had torsade de pointes, but it was also associated with hypokalemia. Also, Roboz et al. [43] in a group of 113 patients observed QT prolongation > 500 ms in 12% of individuals, and none of them showed torsade de pointes.

4.1. Tyrosine Kinase Inhibitors. Nilotinib was associated with 5 to 15 ms QT prolongation, but this prolongation was not associated with polymorphic ventricular tachycardia [56]. On the other hand, in the study of Tam et al. [57], nilotinib administered to healthy volunteers resulted in an average QT prolongation of 18 ms. On subgroup analysis, 1.9% and even 2.5% of patients with chronic myeloid leukemia presented QT prolongation. Of all patients treated with nilotinib from Tam et al.'s study, 0.3% died suddenly, and it was assumed that QT interval prolongation had an involvement, although no direct relationship between had been demonstrated. Lu et al. [58]. have also shown that dasatinib, sunitinib, and nilotinib can prolong the QT interval. Studies with Vandetanib have shown a QT prolongation in 9% to 61% of the patients [59]. In Wells et al.'s [60] and Natale et al.'s [61] studies, QT prolongation occurred in approximately 5.1% of patients; only one of the patients presented torsade de pointes; in all other patients, the QT prolongation had no arrhythmic consequence. In these 2 studies that we have mentioned, the definition of the prolonged QT interval was >550 ms or an increase of >100 ms between 2 consecutive measurements. Zang et al. [62]. performed a systematic review and meta-analysis of Vandetanib' studies related to QT prolongation. They showed that QT prolongation > 450 /460 ms occurred in 16.4% (95% CI 8.1–30.4) of patients and >500 ms prolongation occurred in 3.7% of patients (95% CI 1.7–7.8).

4.2. Histone Deacetylation Inhibitors. Vorinostat has been incriminated in the prolongation of the QT interval complicated with polymorphic ventricular tachycardia in a case report published by Lynch et al. [63]. It is important to mention that the patient associated hypokalemia. Probably hypokalemia, more than chemotherapy, was involved in the development of malignant ventricular arrhythmias, and this patient would have had a congenital long QT syndrome that could have been exposed by vorinostat. However, no genetic study has been done to confirm this hypothesis. Romidepsin has been incriminated in several cases of sudden cardiac death, but there has been no clear relationship between QT prolongation and death, as patients did not have an ECG recording before death [64, 65]. In the study of Piekarz et al. [64], QT prolongation was approximately 15 ms after administration of romidepsin. This prolongation is insignificant and does not justify stopping chemotherapy that might be life-saving. Last but not least, panobinostat is another histone deacetylation inhibitor, which has also been shown to prolong the QT interval up to 20 ms [65]. In conclusion, histone deacetylation inhibitors may prolong the QT interval, but no clear association with arrhythmic events such as torsade de pointes has been demonstrated.

4.3. Anthracyclines. Even though the most common side effect of anthracyclines is structural impairment of the left ventricle with decreased LV ejection fraction, to a lesser extent, anthracyclines may alter the QT interval. In the study of Galetta et al. [18], epirubicin produced variable QT prolongation when administered to patients with non-Hodgkin's lymphoma (all the patients showed increased

QT dispersion (44.3 ± 8.4 vs. 68.4 ± 11.4 ms, $p < 0.001$) and QTc dispersion (46.2 ± 6.2 vs. 72.42 ± 8.4 ms, $p < 0.001$) after epirubicin-based chemotherapy in non-Hodgkin lymphoma patients). Also, in the study of Nousiainen et al. [66], QTc dispersion increased from 26.5 ± 2.5 to 39.0 ± 3.5 ms ($p = 0.039$). Five patients (18%) developed QT dispersion exceeding 50 ms. At the same time, Liu et al. [67] showed in experimental studies on rabbit myocytes that tamoxifen can prolong the QT interval.

5. ECG Changes Produced by Chemotherapy in Children

As in adults, chemotherapy can have cardiac toxicity in children. But children have 2 particularities: First, their heart is constantly developing, and the structure that has been affected by chemotherapy will increase with the growth of the child's heart, so in the following years, the injured structure will become larger [68]. Second, the survival of children is generally higher than that of adults; therefore, on the one hand, it is important to limit the cardiac toxic effect of chemotherapy which will last for years; on the other hand, if the toxic effect occurred, the evolution of left ventricular dysfunction should be blocked to prevent the development of clinical manifest heart failure. As for arrhythmias, they generally appear in the acute phase and disappear after stopping the chemotherapeutic. If arrhythmias occur in the chronic, postadministration phase, then antiarrhythmic drugs are generally needed to control arrhythmias.

Up to 25% of children who are treated with anthracyclines may have electrocardiogram changes [69]. These can be QT interval prolongation, ischemic or nonischemic T-wave and ST segment changes, bundle branch blocks or atrioventricular blocks, decreased QRS complex amplitude, and electric axis change. In addition, atrial or ventricular arrhythmias with different severity ranging from premature contractions to tachycardia were described. In the study of Larsen et al. [70] performed on 100 children with an average age of 15 years, 73 treated with anthracyclines and 27 treated with anthracyclines plus radiotherapy, minor arrhythmias were detected, such as rare atrial or ventricular premature contractions, as well as major arrhythmias. Among these are sustained supraventricular tachycardia or ventricular tachycardia that occurred especially at high doses of anthracyclines $> 200\ mg/m^2$. Furthermore, prolonged QT interval > 480 ms was found in approximately 14% of children. Another study by Steinherz and Steinherz [71] on 100 children identified ECG changes in 13 of them after anthracyclines. One of the 100 died suddenly, without any ECG changes, and 2 died due to arrhythmias. In another study, Lipshultz et al. [72] found 5% nonsustained ventricular tachycardia in children treated with doxorubicin. Amsacrine [73] can also cause ECG changes in children and usually occur within the first minutes or hours of administration. These are QT prolongations, ST and T-wave ischemic changes or nonspecific nonischemic changes, and atrial or ventricular tachyarrhythmias. Usually, these changes occur from the first dose and can be quickly detected by ECG. If the patient has an underlying hypokalemia, then the depolarization and repolarization changes given by amsacrine may be exacerbated by hypokalemia, so serum potassium levels should be monitored during therapy.

Massin et al. [74] studied severe arrhythmias that occur in the first 24 hours in 33 children with various tumors treated with chemotherapy. Two patients developed sinoatrial block or atrioventricular block during the first 4 hours of daunorubicin infusion, 8 children had atrial and ventricular premature beats or bursts of premature beats during the combination of vincristine+daunorubicin or vincristine+cyclophosphamide, and none of the children presented life-threatening arrhythmias.

In a study by Mulrooney et al. [75], 2715 children who survived neoplastic disease have been checked for ECG changes, which were interpreted as chronic side effects due to chemotherapy. Thus, 99 individuals were identified with pathological Q-waves as signs of old myocardial infarction, 5 with left branch block, 13 with right branch block, 4 with bifascicular block, 8 with significant QT prolongation, and none with atrial flutter or atrial fibrillation. In total, major ECG changes were present in 290 of 2715 patients (approximately 10%) and minor ECG changes in 565 (23.3%). Minor changes included atrial or ventricular premature beats, nonspecific T-wave or ST segment changes, low QRS, and deviation of the heart's electrical axis.

Newer studies are trying to determine whether lower chemotherapy doses that do not induce ECG changes still remain effective for the suppression of neoplastic disease. Researchers are trying to verify if lower doses that do not cause an excessive increase in QT interval > 480 ms or that produce only benign atrial or ventricular premature beats are still effective in controlling the child's neoplastic disease. The results of the studies would further benefit children, as toxic effects might affect a developing, immature heart.

6. Conclusions

Oncological treatment requires a good collaboration between the oncologist and the cardiologist. Even if new drugs increase the life expectancy of cancer patients, death may be due to a therapeutic dosing error, due to proarrhythmic side effects, or due to impaired left ventricular ejection fraction. For these reasons, some oncology clinics have hired a cardiologist who can monitor the evolution of heart function during chemotherapy by ECG, Holter ECG, and echocardiography. The cardiologist must know the limits that are acceptable for subclinical cardiac toxicity such as a mild but reasonably prolonged QT interval below 480 ms, the presence of benign arrhythmias such as atrial or ventricular premature beats, the presence of insignificant ST segment and T-wave changes, and changes in the heart axis. All of these ECG insignificant changes should not stop the child or adult from receiving a potentially life-saving therapy. When the oncology-cardiologist is not available, close collaboration with a cardiology clinic or outpatient cardiac clinic with experienced physicians in monitoring toxic effects of chemotherapy is required.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Review Article

Cardiotoxicity: A Major Setback in Childhood Leukemia Treatment

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Ongoing research in the field of pediatric oncology has led to an increased number of childhood cancer survivors reaching adulthood. Therefore, ensuring a good quality of life for these patients has become a rising priority. Considering this, the following review focuses on summarizing the most recent research in anthracycline-induced cardiac toxicity in children treated for leukemia. For pediatric cancers, anthracyclines are one of the most used anticancer drugs, with over half of the childhood cancer survivors believed to have been exposed to them. Anthracyclines cause irreversible cardiomyocyte loss, leading to chronic, progressive heart failure. The risk of developing cardiotoxicity has been known to increase with the treatment-free interval and total cumulative dose. However, because of individual variations in anthracycline metabolism, it has recently been shown that there is no risk-free dose. Moreover, studies have shown that diagnosing anthracycline-induced cardiomyopathy in the symptomatic phase is associated with poor treatment response and prognosis. Thus, early and systematic evaluation of these patients is crucial to allow optimal therapeutic intervention. Although currently echocardiographic assessment of left ventricle ejection fraction and cardiac biomarker evaluation are being used for cardiac function monitoring in oncologic patients, there is no established follow-up and treatment protocol for these patients, and these methods are neither specific nor sensitive for identifying early cardiac dysfunction. All things considered, the need for ongoing research in the field of pediatric cardiooncology is crucial to offer these patients a chance at a good quality of life as adults.

1. Introduction

Recent discoveries in the field of pediatric oncology have significantly improved 5-year survival rates, from 50% in the 1970s to 80% nowadays [1–4]. On the other hand, the incidence of pediatric cancers is slowly increasing [5], most noticeable for leukemia, cancer being still one of the main causes of death by illness in childhood and adolescence [1–3]. Hematopoietic malignancies are the most common cancers in children, accounting for up to 31% of all malignancies that occur in children younger than 15 years of age [1, 3, 6]. Leukemias are more common than lymphomas; the most common is acute lymphoblastic leukemia (ALL), representing up to 25% of all childhood cancers in children under 15 years old [7]. The most important prognostic factor is the correct choice of treatment based

on specific group stratification. Risk assessment takes into account many factors including leukemia subtype, age and white blood cell count at diagnosis, and also response rate to the induction treatment [7, 8]. Chemotherapy is the main treatment method used in leukemia and consists of an association of several cytotoxic agents, showing an increased efficiency of up to 85% in inducing remission [3, 6].

However, efficient, oncological treatments are often aggressive, with multiple side effects that can also occur years after treatment has ended. Considering that more survivors of childhood cancer reach adulthood, special attention has been given to the quality of life of these patients, as well as to the late-onset complications of the antineoplastic treatment [2, 3, 6]. Better knowledge and understanding of these side effects are needed to amend or even prevent some of them in the future. Cardiovascular complications are one of the main causes of morbidity and mortality in survivors of childhood cancer [9, 10]. Anthracyclines (AC) represent one of the most effective chemotherapeutic agents currently used, being simultaneously the most well known for their effects on the cardiovascular system [11]. The Childhood Cancer Survivor Study (CCSS) has shown that the risk of death due to cardiovascular disease is eight times higher in survivors of an AC-treated neoplasm as compared to the general population [12, 13]. Considering the unfavorable prognosis of AC-induced cardiomyopathy [14], early identification of patients at risk by means of optimal cardiac function monitoring is essential both for the cardiologist and the oncologist, allowing timely implementation of personalized treatment regimens and possibly even prevention of cardiac dysfunction.

2. Chemotherapy-Induced Cardiotoxicity

2.1. General Toxicity. As stated, chemotherapy is the main method used for the treatment of pediatric leukemia. Although an effective treatment, one of its major drawbacks is the increased toxicity of the drugs being used, which sometimes counterbalances their therapeutic benefit [9–11, 15].

Anticancer drugs have general toxicity, explained by their action on cells with a high division rate, such as intestinal epithelia and hematopoietic cells. Thus, the most common side effects are bone marrow failure, digestive disorders (nausea, vomiting, and diarrhoea), and alopecia. These consequences cannot be avoided but in most cases resolve spontaneously when stopping the treatment. Specific toxicity is determined by the pharmacodynamics and pharmacokinetic particularities of each agent used.

In order to determine the life quality of cancer survivors, CCSS has monitored cancer treatment side effects on 14,357 survivors of pediatric malignancies treated between 1970 and 1986, with at least 5 treatment-free years at the moment of enrolment in the study. Analyzing the data, it has been found that survivors of childhood cancer have an eight times higher risk of developing chronic diseases as compared to their brothers or sisters. Also, more than a third will eventually develop a severe, potentially fatal condition [13]. In addition to the development of secondary malignancy, the most common side effects associated with the use of chemotherapies are cardiovascular disease, respiratory dysfunction, renal failure, infertility, psychosomatic development delay, and allergic reactions [13, 15, 16].

2.2. Cardiac Toxicity. The heart is a tissue with reduced regenerative capacity, so any extensive injury will cause irreversible damage. Although recent research has led to the development of even more effective antineoplastic agents, their effects on the myocardial tissue have not disappeared.

Cardiovascular side effects caused by chemotherapy are various, including arrhythmias and conduction disorders, heart failure (HF), acute coronary syndromes, myocarditis, and pericarditis. The most commonly encountered side effect is the alteration of left ventricular (LV) contractility, with the consequent decrease of its ejection fraction (LVEF).

In a simplified manner, postchemotherapy cardiotoxicity has been divided into two types: type I: caused by cardiomyocyte death, irreversible (most commonly associated with AC treatment), and type II: caused by myocardial dysfunction, frequently reversible (most commonly associated with Trastuzumab use) [17].

AC-induced cardiac dysfunction can also be divided into clinical and subclinical disease, by taking into account the presence or absence of clinical manifestations of congestive HF. In terms of subclinical changes, multiple definitions have been proposed, a widely accepted one being an alteration of the systolic function objectified by echocardiographic measurements or radionuclide angiography. Concerning the echocardiographic criteria, systolic dysfunction is considered to be present when LVEF is reduced by 10% for asymptomatic patients and 5% in symptomatic patients, or a decrease of LVEF below 50% [18].

2.3. Anthracycline-Induced Cardiac Toxicity. It is estimated that there are currently over 363,000 survivors of childhood cancer, with 60% of them believed to have been exposed to AC [19].

2.3.1. Anthracyclines: The Mechanism of Toxicity. AC are a class of anticancer drugs, derived from Streptomyces Bacterium. They act at the nuclear level by DNA intercalation, topoisomerase 2β (TOP2β) inhibition, and production of reactive oxygen species (ROS), eventually triggering the pathways of cellular apoptosis [14, 20, 21]. Of all the classes of anticancer drugs used in the treatment of pediatric leukemia, AC are most known for their toxic effects on cardiac tissue [14, 18, 19]. These are effective antimitotics on many types of cancer, doxorubicin (DOX) being the most potent agent in this class, with the largest action spectrum. It is commonly used in oncology for both solid tumors and hematopoietic malignancies. However, the proven cardiac side effects of both DOX and daunorubicin limit their use [22]. More novel AC molecules such as Epirubicin and idarubicin and the structurally related molecule mitoxantrone have been proposed as less cardiotoxic variants of DOX. However, over the years, all types of AC have been shown to cause AC-induced cardiac toxicity [23].

The molecular mechanism for AC-induced cardiotoxicity (Figure 1) is complex and incompletely understood: cardiac toxicity is believed to be caused partly by the production of ROS and partly by the production of alcohol metabolites that accumulate in the myocytes [20].

Considering DOX, for example, the reduction of an electron from the quinone group leads to the formation of a semiquinonic radical, which will reduce the molecular oxygen to superoxide anion and hydrogen peroxide, both ROS. In this way, DOX causes oxidative stress and energy depletion at the cellular level, while also activating apoptotic pathways. Consequently, AC induce irreversible cardiomyocyte loss.

The second mechanism proposed, which explains the chronic, ongoing damage suffered by the myocardium, involves the conversion of AC to alcohol metabolites. These do not have the same oxidative potential as ROS but cause disturbances in calcium (Ca) and iron (Fe) cellular homeostasis, thereby affecting the contractile function. Also, being polar compounds, alcohols accumulate, which explains why cardiotoxicity risk increases proportionally to the total administered dose of AC [20, 21, 24].

Recent studies propose that TOP2β is involved in the development of increased oxidative stress following DOX treatment. AC bind to both TOP2α, which is overexpressed in cancerous cells, and TOP2β, expressed in adult mammalian cardiomyocytes. Studies showed that TOP2β cardiomyocyte knockout mice presented less impairment in cardiomyocyte function, while wild-type mice exhibited significant abnormalities in the p53 tumor suppressor gene, β-adrenergic signaling, and apoptotic pathways. [25]

The more the mechanisms of cardiotoxicity are understood, the easier it becomes to develop new cardioprotective treatment strategies, while also preserving the desired oncologic efficacy.

2.3.2. Risk Factors for the Development of Anthracycline-Induced Cardiotoxicity. The incidence of cardiotoxicity after AC treatment is influenced by multiple factors, among the most important ones being the type of chemotherapy, the total given dose, and age at onset of therapy [26].

As stated, AC are one of the antineoplastic medications most frequently associated with long-term cardiac side effects following chemotherapy, the risk increasing proportionally to the total cumulative dose. At a total dose of less than 300 mg/m^2, the risk of developing cardiotoxicity is considered to be 5%, increasing to 20% when the total dose exceeds 300 mg/m^2 and to more than 35% at doses higher than 600 mg/m^2 [27].

In the pediatric population, young age at diagnosis has been associated with an increased risk of subsequent cardiac damage. A study by Armstrong and Ross showed that childhood cancer survivors had twelve times higher risk of developing congestive HF following AC treatment in the following 3 years after treatment [28]. Also, another study showed that the incidence of AC-induced cardiac toxicity has risen up to 30% of the adult survivors of childhood cancer [29].

Other risk factors for AC-induced cardiac toxicity are preexisting cardiovascular risk factors such as diabetes, arterial hypertension, obesity, lung disease, or thyroid disease [30]. This is why, in the adult population, an increase in cardiotoxicity following AC treatment is noticed with age, as the elderly population already presents an increased prevalence of the above-mentioned additional cardiac risk factors.

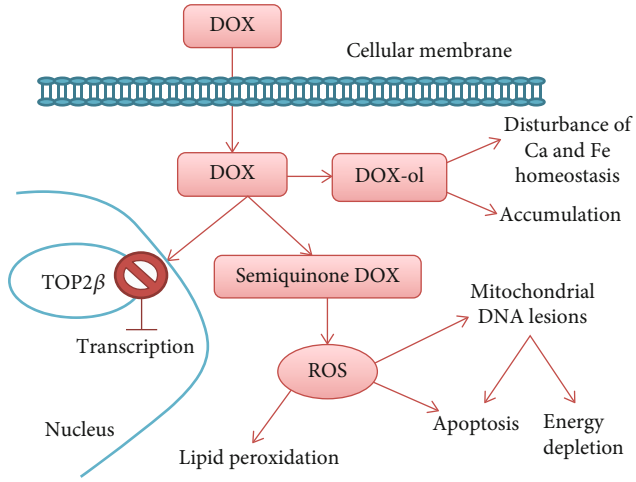

Figure 1: Doxorubicin (DOX): mechanism of action (DOX alcohol metabolites: DOX-ol).

2.3.3. Clinical Manifestations: Prognosis. Cardiovascular complications caused by AC can be acute, chronic with early onset or chronic with late onset, depending on the time frame and reversibility of cardiac damage [9].

Acute toxicity occurs rarely during treatment, with an incidence lower than 1%, is dose-independent, and most often resolves shortly after treatment ends [31]. It may have various manifestations: myocarditis, pericarditis, and endocarditis. Acute HF during treatment is a rare but extremely serious side effect, as it requires immediate treatment termination [32]. Arrhythmias and hypotensive episodes are acute manifestations that occur more often during treatment but do not always require cessation of chemotherapy [9].

Chronic heart disease is a more common side effect of AC treatment. Depending on the onset of symptoms, cardiac damage may be subdivided into early-onset cardiotoxicity when symptoms occur within 1 year from finalizing the treatment or cardiotoxicity with late onset when symptoms occur after more than 1 year from finishing chemotherapy. The risk of developing cardiac toxicity increases proportionally to the treatment-free interval [33, 34]. Chronic cardiotoxicity manifests as a decrease in cardiac function leading to CHF. Unlike acute complications, chronic impairment is in most cases progressive [9, 10]. This toxicity has been shown to be dose-dependent and cumulative: initially, diastolic dysfunction occurs with a cumulative doxorubicin dose of 200 mg/m^2, while systolic dysfunction occurs later, when the total dose exceeds 400-600 mg/m^2, with individual variability [32, 33]. However, recent studies have shown that cardiac toxicity can occur even at doses previously considered "harmless" to cardiac tissue [35, 36].

Diastolic dysfunction is frequently asymptomatic, which is why careful cardiac monitoring of patients treated with

anthracyclines is required even if they do not present any symptoms of cardiac disease [33]. Also, if diagnosed in the symptomatic phase, the prognosis and treatment response of AC-induced cardiomyopathy are poor with a 5-year survival rate below 50% [33, 37].

2.3.4. Genetic Polymorphisms in Anthracycline Metabolism. A long-term follow-up of anthracycline-treated children has shown in some patients development of cardiac side effects at cumulative doses of less than 150 mg/m^2, as well as a lack of toxic effects in some patients at over 600 mg/m^2 [35]. This indicates the importance of individual variability in terms of pharmacodynamics and pharmacokinetics, most likely due to genetic polymorphisms.

In a recent study, the Children Oncology Group (COG) has shown that homozygous patients for the G allele of carbonyl reductase 3 (CBR3: an oxidoreductase involved in the reduction of carbonyl groups in alcohol groups, important in anthracycline metabolism) are at an increased risk of developing toxic cardiomyopathy even when low doses of AC are being used [38]. For these patients, it is considered that there is no risk-free dosage. Another study identified the polymorphisms of the SLC28A3 gene as an important modulator for the risk of developing AC-related cardiotoxicity [39].

A recent review on AC-related cardiotoxicity mechanisms and genomics in childhood cancer survivors revealed a total of 18 genes or genetic variants associated with AC-induced cardiac toxicity. These genes play roles in DNA damage pathways, oxidative stress response, iron metabolism, drug transport, and sarcomere function. Mostly, the ABCC, CBR3, and SLC28A3 genes have emerged in the majority of studies cited, emphasizing their important role in the development of AC-related heart disease [23].

These findings could facilitate, in the future, the implementation of targeted and personalized primary prophylactic strategies.

3. Monitoring Patients with Anthracycline

The risk of death by cardiovascular pathology is eight times greater in cancer survivors than the risk of tumor recurrence, especially in pediatric patients [9]. Cardiovascular damage dramatically reduces not only the duration but also the quality of life of these patients. Moreover, their response to standard cardiac treatments is often reduced and unsatisfactory.

Diagnosing cardiac toxicity at a stage where it is already symptomatic greatly limits the potential benefits of drug intervention, thus the importance of establishing a method that could aid in diagnosing AC-induced cardiomyopathy in its subclinical stages. This can be achieved by elaborating a specific follow-up protocol using the means we currently have, as well as developing new methods for early identification of patients at risk [27].

3.1. Echocardiography. Echocardiography is the most commonly used screening method for cardiac pathology, being an easily accessible, noninvasive, inexpensive, and fast method that allows real-time visualization of the heart.

Evaluation of the LVEF is essential for assessing heart function, being also a necessary tool in the diagnosis of AC-induced cardiomyopathy [27, 33]. Some studies also recommend the use of ventricular shortening fraction (SF) during the follow-up, with a SF lower than 30% indicating significant cardiac function impairment [40, 41].

However convenient, studies have shown that changes in LVEF or LVSF often show a rather irreversible alteration of heart function [32, 41]. Therefore, the European Society for Medical Oncology (ESMO) proposed the use of Doppler echocardiography for basal evaluation and periodic monitoring of cardiac function [42] as being a more sensitive method. What is more, the Pulse Wave Doppler (PWD) method has proven to be extremely useful, allowing for the assessment of flow velocities at a given point in real time. The PWD method records the magnitude of E and A waves at the level of the mitral valve, the ratio of which (E/A) is useful in diagnosing diastolic dysfunction.

Recently, Tissue Doppler Imaging (TDI) has become increasingly used, allowing diagnosis of cardiac impairment even in the stage of subclinical diastolic dysfunction. This method records myocardium motion velocities with the pulsed Doppler system set for low velocities. Using TDI, 3 wave patterns are recorded: the positive S' wave (recorded in the systolic phase) and the negative E' and A' waves (recorded in the diastolic phase). Studies showed decreased rates of these waves in the AC-treated group versus the control group [43, 44]. These correlated with reduced systolic contraction and delayed relaxation, in apparently asymptomatic patients with normal LVEF and LVSF. This emphasizes the importance of using PWD and TDI for the timely detection of cardiac dysfunction.

Another method of identifying early cardiac damage is speckle tracking. This is an application of TDI, which calculates the strain and strain rate based on spatial differences in tissue velocity. Follow-up studies of oncological patients encourage evaluation of LV strain and global strain, the latter being preferred. However, these evaluations proved to be more useful in the immediate period following treatment and less in the long-term follow-up [45]. A recent study of 1,820 surviving, adult, pediatric cancer patients revealed a reduction in global longitudinal strain (GLS), as compared to normal values. However, the patients included in this study already had low LVEF, hypertension, or impaired glucose tolerance; therefore it was not possible to determine if GLS was reduced merely because of the former antineoplastic treatment [46].

Lastly, echocardiography greatly depends on the operator, the results being greatly influenced by their knowledge. All things considered, the ideal imaging method of cardiac function evaluation for these patients is still to be determined.

3.2. Electrocardiogram (ECG). ECG is a noninvasive method used to evaluate cardiac conductive tissue, allowing identification of arrhythmias, conduction anomalies, and cardiac ischemia. There are studies that correlated a prolonged QT interval in oncological patients with the increased possibility of later developing a cardiac pathology [47]. Acute DOX

toxicity includes supraventricular tachycardia, ventricular ectopy, myopericarditis, cardiomyopathy, and death. However rare, these manifestations are life-threatening; thus, ECG examination is required in the follow-up protocol of these patients.

3.3. Biomarkers. In recent years, interest in the use of biological markers has increased due to the need to easily identify patients at risk of developing chemotherapy-related cardiac toxicity.

3.3.1. C-Reactive Protein (CRP). CRP is an acute-phase protein synthesized in the liver. In patients with heart disease, high levels of CRP signal a proinflammatory status and correlate with the HF severity, indicating a negative prognosis. Also, highly sensitive CRP (hs-CRP) is a reliable indicator for the risk of an acute cardiovascular event, values higher than 3 mg/l being associated with an increased risk [27].

3.3.2. Tumor Necrosis Factor Alpha (TNFα). TNFα, Interleukin- (IL-) 1, IL-6, and IL-18 are proinflammatory cytokines. IL-6 induces myocardial hypertrophy, while TNFα activates matrix metalloproteinases, inducing LV dilatation. The two cytokines have been used as predictive markers for the development of HF in elderly patients [48].

3.3.3. Markers of Oxidative Stress. Since it is difficult to assess cellular oxidative stress, it was attempted to estimate it using indirect markers such as oxidized low-density lipoproteins, malondialdehyde, and myeloperoxidase. In animal models, administration of doxorubicin increased both the activity of myeloperoxidase and lipid peroxidation [49].

3.3.4. Natriuretic Peptides. Brain natriuretic peptide (BNP) and N-terminal prohormone BNP (NT-proBNP) are two extremely useful markers in cardiac function assessment. These are synthesized in the myocyte in response to increased cardiac wall pressure. BNP produces vasodilatation, increases diuresis and natriuresis, and reduces sympathetic nervous system activity and renin-angiotensin-aldosterone system activation. They are used to diagnose HF (at a level above 400 pg/ml), to stratify the patients in risk groups, and also in their long-term follow-up [50].

Recently, the utility of these markers has been demonstrated for identifying patients at risk of developing cardiotoxicity. In a study by Sandri et al., 52 patients who received high-dose chemotherapy were evaluated. NT-proBNP values were determined at onset and at the end of treatment, as well as at 12, 24, 36, and 72 hours after. The values of 33% of patients remained elevated and 72 hours posttreatment. This group demonstrated a decrease in LV diastolic index and a reduction in LVEF from 62% to 45% in the year following treatment [51].

3.3.5. Markers of Myocardial Injury. Cardiac Troponins (cTn) T and I are myofibrillar proteins that have demonstrated increased sensitivity and specificity as markers of myocardial injury. Several studies have shown increased cTnT levels in the early stages of AC therapy [52]. This increase was correlated in some studies, with a marked reduction in the diastolic function of LV [53, 54]. In a study on patients with breast cancer treated with Trastuzumab, cTnI has proven to be an important predictor of cardiotoxicity as well as a negative prognostic factor regarding cardiac function recovery [18]. Following these studies, in 2010, Cardinale and Sandri proposed cTn levels to be used in cardiac risk assessment for both standard anticancer treatments and new biological therapy [54]. Also, in a study of 18 pediatric patients diagnosed with non-Hodgkin's lymphoma, Blaes et al. showed that patients with elevated cTn at the beginning of treatment had an increased incidence of systolic dysfunction [55].

A recent review analyzing over 20 studies regarding cTn use as a biomarker of cardiotoxicity in patients treated with AC for breast cancer concluded that the main evidence up until today is that low cTn levels during treatment correlate with a better long-term prognosis regarding heart function [56].

3.4. Monitoring during Treatment. Monitoring during treatment has a role of identifying potential cardiac damage as soon as possible, thus allowing therapeutic interventions and treatment modification. The goal is to reduce the risk of developing long-term cardiac complications [11]. At the same time, it should be taken into account not to reduce treatment's efficacy, which would eliminate the benefit created by reducing cardiotoxicity.

A recent study on pediatric leukemia has shown that myocardial tissue is affected even before chemotherapy begins, as seen from the correlation determined between the white blood cell count at diagnosis and NT-proBNP values. This might be partially explained by myocardial infiltration with cancer cells. However, preexisting cardiac suffering highlights even more the need for a timely, rigorous, ongoing cardiac function evaluation [57].

In order to be effective, Steinherz et al. emphasize the importance of conducting an ECG and echocardiography prior to the beginning of treatment [58]. Subsequently, most guidelines recommend an ultrasound after half the total cumulative dose of doxorubicin is given, followed by an echocardiographic examination before each of the following doses [58]. It has been proposed that at a decrease in LVEF below 50% or more than 10% during treatment, chemotherapy should be discontinued. This is based on the fact that the identified systolic dysfunction appears most likely following an extensive myocardial injury [27]. However, a lack of reduction in LVEF during treatment does not rule out the possibility of late cardiac toxicity [27, 33, 43, 59].

3.5. Long-Term Monitoring. Lifetime screening for cardiac damage is indicated following antineoplastic treatment, especially in patients treated with AC or those who have received radiation therapy to the chest.

In the first year following treatment, ultrasound screening is currently recommended at 3, 6, and 12 months [26]. COG provides a detailed guide on the frequency of posttreatment monitoring, based on age at exposure to AC, the total dose received, and the association with thoracic irradiation.

For a universal approach, they propose converting all doses of AC to isotoxic doses of doxorubicin [38].

Another important aspect is the screening for cardiovascular risk factors: sedentary lifestyle, tobacco use, family history of premature coronary heart disease (less than 55 years in men and 65 years in women, respectively), lipid profile, basal blood glucose, and blood pressure (BP). Cancer patients are generally considered at risk for development of cardiovascular pathology, so adding any other two cardiac risk factors leads to the inclusion of these patients in a high-risk group. Thus, according to the American Heart Association, for cancer survivors, the target body mass index (BMI), BP, LDL, and glucose levels change: BMI < 90th percentile, BP < 95th percentile, LDL < 130 mg/dl, and basal blood glucose < 100 mg/dl [60].

4. Therapeutic Outlook for Anthracycline-Induced Heart Failure

First of all, in order to decrease the likelihood of AC-induced cardiac disease, the administration recommendations have been modified. The maximum total cumulative dose recommended nowadays being 400-550 mg/m^2 DOX and 900 mg/m^2 Epirubicin. Anyhow, one must keep in mind that up until now no dose of AC has been considered cardiac risk-free, so the ongoing evaluation of these patients is mandatory regardless of the received dose. Also, a slow DOX infusion has proven to diminish the cardiotoxic effect of AC use, by lowering its maximum plasma levels, a parameter which, in turn, determines the amount of drug entering the myocardial tissue [61]. However, Lipshultz et al. conducted a study on 102 children treated for ALL, who received doxorubicin in a randomized fashion, either in a continuous regimen (over 48 hours) or by bolus (15 minutes). A cardiac follow-up, with a median of 8 years, showed no significant difference in cardiac function between the two groups, concluding that, in children, continuous infusion shows no benefit over bolus administration [62].

The use of liposomal drug formulations has been widely debated and studied. Liposomal DOX has the advantage of a limited diffusion through the myocardial tissue, due to their size (too big to cross the endothelial junction of healthy tissues) with preserved antitumor efficiency (leaky, irregular tumor vasculature) [63]. There are many successful animal studies done on solid tumors, which show not only the preserved desired antitumor effect with minimal cardiac toxicity but also, in some cases, liposomal formulations actually exposing tumor cells to higher amounts of AC [64]. However good the results are, there are few randomized clinical trials on liposomal-coated AC, thus the limited clinical indications so far being metastatic breast cancer, advanced ovarian cancer, multiple myeloma, and AIDS-related sarcoma [65]. Until further studies emerge, liposomal formulations are not yet an alternative for children with leukemia.

Regarding preventive treatment, cardioprotective drugs such as dexrazoxane, angiotensin-conversion enzyme inhibitors, and beta-blockers have been tested [21, 66]. Dexrazoxane, an iron chelating agent, has long been considered the first-line prophylactic therapy for chemotherapy-induced cardiac toxicity, being the only drug currently approved by the US FDA for the prevention of AC-induced HF. It has also been proven to be efficient in children with leukemia. Lipshultz et al. demonstrated in a randomized controlled trial of 205 children the protective effect of dexrazoxane on cardiac function as means of LV structure and function, with no adverse effect on relapse risk, frequency of secondary malignancy, or survival [67]. Another randomized controlled trial, from the Pediatric Oncology Group, has shown that, although the 5-year survival rate did not differ between the group that received dexrazoxane and the group without it, measurements of the SF, LV wall thickness, and thickness-to-dimension ratio were worse in patients who did not receive dexrazoxane [68]. However, in 2007, a controversial study claimed that dexrazoxane use could increase the risk of secondary malignancies, especially AML [69]. No further studies have supported this theory so far [70]. What is more, after previously allowing dexrazoxane to be used only in women treated for breast cancer, the EMA changed its decision and now supports its administration to pediatric patients who are likely to be treated with high cumulative doses of anthracyclines (>300 mg/m^2 of doxorubicin) [71, 72].

Beta-blocker use is encouraged in a recent review on their role in the prevention of AC-induced cardiotoxicity, due to their important cardioprotective action. Carvedilol seems to be the most studied drug from this class; however, its dosing regimens and optimal timeline of administration in oncologic patients still need to be established [73]. A small study of 25 patients demonstrated that Carvedilol administration started before initiating AC therapy improved LVEF and the value of the *E*/*A* ratio compared to the placebo group [74]. Similar studies were also performed using Enalapril, Spironolactone, Metoprolol, and Candesartan, all with encouraging results in the prevention of postchemotherapy cardiotoxicity [75–78]. Another study conducted on 473 cancer patients presenting with elevated cTn following various cytostatic regimens demonstrated that Enalapril administration for over a year resulted in a lower incidence of LV dysfunction than in the placebo group [79].

For patients who have already developed HF secondary to cytostatic treatments, there are limited studies regarding the appropriate therapeutic approach. For now, HF is to be treated according to the current guidelines, although treatment response is poorer than in the "classical" HF patient population.

5. Conclusion

Taking all the above-mentioned aspects into account, it is obvious that cardiotoxicity following AC treatment is a current issue for both the oncologist and the cardiologist. The pediatric population represents an even bigger challenge, because of the various stages of development in which children receive chemotherapy, being very difficult to establish specific monitoring and treatment protocols. There are many questions unanswered in cardiooncology, thus the need and development of a separate medical specialty dealing with this intricate problem. All things considered, careful and

systematic monitoring, as well as timely intervention, proves to be crucial to the long-term prognosis and quality of life for these patients.

Data Availability

The data supporting this review are from previously reported studies and datasets, which have been cited.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Authors' Contributions

Diana R. Lazăr conceived and designed the analysis, collected the data, contributed with data or analysis tools, and wrote the paper. Anca D. Farcaș wrote the paper, gave feedback, and updated the version of the paper. Cristina Blag, Alexandra Neaga, and Mihnea T. Zdrenghea contributed with data or analysis tools. Călin Căinap conceived and designed the analysis, contributed with data or analysis tools, and wrote the paper. Florin L. Lazăr collected the data and contributed with data or analysis tools. Adrian Stef gave other contributions in the modified version of the article after reviewers' comments. Simona S. Căinap conceived and designed the analysis, contributed with data or analysis tools, performed the analysis, and wrote the paper. Diana R. Lazăr is the first author and should be regarded as such. Călin Căinap has/shares the same contribution as the first author and should be regarded like this.

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Research Article

Genetic Variability of Antioxidative Mechanisms and Cardiotoxicity after Adjuvant Radiotherapy in HER2-Positive Breast Cancer Patients

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Background. Breast cancer treatment is associated with the occurrence of various cardiac adverse events. One of the mechanisms associated with cardiotoxicity is oxidative stress, against which cells are protected by antioxidative enzymes. Genetic variability of antioxidative enzymes can affect enzyme activity or expression, which modifies the ability of cells to defend themselves against oxidative stress and could consequently contribute to the occurrence of treatment-related cardiotoxicity. Our aim was to evaluate the association of common polymorphisms in antioxidative genes with cardiotoxicity after adjuvant radiotherapy (RT) in HER2-positive breast cancer patients. *Methods*. Our retrospective study included 101 HER2-positive early breast cancer patients who received trastuzumab and adjuvant RT. We isolated DNA from buccal swabs and used competitive allele-specific PCR for genotyping of *PON1* rs854560 and rs662, *GSTP1* rs1138272 and rs1695, *SOD2* rs4880, *CAT* rs1001179, and *HIF1* rs1154965 polymorphisms. N-terminal pro B-type natriuretic peptide (NT-proBNP), left ventricular ejection fraction, and NYHA class were used as markers of cardiotoxicity. We used logistic regression to evaluate the association of genetic factors with markers of cardiotoxicity. *Results*. Carriers of at least one polymorphic *PON1* rs854560 allele were less likely to have increased NT-proBNP (OR = 0.34; 95% CI = 0.15-0.79; $P = 0.012$), even after adjustment for age (OR = 0.35; 95% CI = 0.15-0.83; $P = 0.017$). Carriers of at least one polymorphic *PON1* rs662 allele were more likely to have increased NT-proBNP (OR = 4.44; 95% CI = 1.85-10.66; $P = 0.001$), even after adjustment for age (OR = 5.41; 95% CI = 2.12-13.78; $P < 0.001$). *GSTP1* rs1695 was also associated with decreased NT-proBNP in the multivariable analysis ($P = 0.026$), while *CAT* rs1001179 was associated with NYHA class in the univariable ($P = 0.012$) and multivariable analysis ($P = 0.023$). *Conclusion*. In our study, polymorphisms *PON1* rs662 and rs854560, *CAT* rs1001179, and *GSTP1* rs1695 were significantly associated with the occurrence of cardiac adverse events after adjuvant RT and could serve as biomarkers contributing to treatment personalization.

1. Introduction

Adjuvant radiotherapy (RT) has significantly improved disease-specific survival for patients with early-stage breast cancer [1, 2]. As a consequence, more cancer survivors may experience late complications of treatment [3]. Radiation dose received by the heart during adjuvant RT of breast or thoracic wall may result in a range of cardiotoxic effects including coronary artery disease, cardiomyopathy, pericardial disease, valvular dysfunction, and conduction abnormalities [4, 5]. There is no minimum radiation dose to the heart that is entirely safe [4].

A combination of adjuvant RT and systemic oncological treatment may have an even worse impact on the cardiac-

related outcome [6]. This combination is frequently used in HER2-positive breast cancer, a subtype of breast cancer with amplification or overexpression of the human epidermal growth factor receptor 2 (HER2) oncogene, which represents approximately 15% of all breast cancers [7, 8]. In standard clinical practice, this subtype of breast cancer is treated with a least two types of cardiotoxic systemic treatment [7, 9]. Anthracyclines are prescribed as a part of neoadjuvant or adjuvant chemotherapy and are followed by anti-HER2 treatment with trastuzumab, a monoclonal antibody [9]. Both types of treatment increase the survival of HER2-positive breast cancer patients but are cardiotoxic [10–13]. Anthracycline-related cardiotoxicity results, at least to some degree, in myocyte destruction and clinical heart failure and is irreversible. Trastuzumab-related cardiotoxicity is most often manifested by an asymptomatic decrease in left ventricular ejection fraction (LVEF) and less often by clinical heart failure [13–15].

Different biomarkers and imaging techniques and their potential role in monitoring cardiotoxicity have already been evaluated [6]. The use of blood-based biomarkers to detect radiation or systemic treatment-induced cardiotoxicity is very promising as it is minimally invasive, affordable, and repeatable [16]. Currently, the determination of LVEF and N-terminal pro-brain natriuretic peptide (NT-proBNP) is mostly used for monitoring cardiotoxicity of cancer treatment [14, 17, 18]. LVEF is the golden standard for monitoring cardiac function in patients receiving cardiotoxic therapy. Echocardiography and radionuclide ventriculography are imaging techniques that are being most widely used in this setting for the assessment of LVEF [14].

Brain natriuretic peptide (BNP), a member of the family of natriuretic hormones, seems to be one of the most appropriate biomarkers for cardiotoxicity evaluation [19, 20]. After being synthesized, its inactive form is then cleaved into active BNP and inactive NT-proBNP. NT-proBNP is a sensitive biomarker of both systolic and diastolic heart failure [21]. NT-proBNP was also an early and sensitive diagnostic and prognostic biomarker for the evaluation of cardiotoxicity of cancer chemotherapy and RT [20, 22, 23]. Patients with elevated NT-proBNP had a higher possibility of asymptomatic LVEF reduction or developing symptomatic heart failure later on. Because changes in NT-proBNP usually occur earlier than changes in LVEF, its elevated level exposes patients at higher risk.

One of the molecular mechanisms associated with cancer treatment response and occurrence of adverse events is oxidative stress. Oxidative stress occurs as a result of excess formation of reactive oxygen species (ROS) that can cause a variety of cellular damage, including DNA modifications, breaks, deletions and translocations, lipid peroxidation, amino acid modifications, and protein conformational changes [24]. Oxidative stress is also among the key stimuli leading to carcinogenesis [25]. RT can trigger oxidative stress in cancer cells, causing DNA damage and stress response activation in mitochondria and the endoplasmic reticulum. Increased ROS formation affects both cancer and surrounding healthy cells, leading to various adverse events, including cardiotoxicity [26, 27]. Oxidative stress was also proposed as one of the mechanisms involved in anthracycline and trastuzumab cardiotoxicity [28–30]. Anthracyclines increase ROS formation through various enzymatic and nonenzymatic reactions [28, 30]. For example, the reduction of anthracyclines results in the formation of semiquinone free radicals and increased formation of ROS through different enzymes. Anthracyclines also interact with ferric iron, leading to altered redox-cycling and the formation of superoxide anion [30]. Trastuzumab is associated with increased ROS formation, decreased glutathione concentration, and decreased activity of antioxidative enzymes in cell lines [31]. Studies suggest trastuzumab mostly affects oxidative stress due to dysregulated HER2 signalling through mitogen-activated protein kinase, phosphoinositide 3-kinase, and neuregulin signalling pathways leading to increased ROS formation [29, 30].

Antioxidative enzymes are part of the cellular mechanisms maintaining appropriate levels of ROS and could therefore affect treatment-related cardiotoxicity. Among them are glutathione-S-transferases (GSTs), crucial for detoxification of endogenous and exogenous substrates by conjugation with reduced glutathione. The most important subtypes are GSTM1, GSTT1, and GSTP1 [32]. The enzyme superoxide dismutase (SOD) catalyzes the conversion of superoxide radical to hydrogen peroxide [33], after which the latter can be converted to water, catalyzed by the enzyme catalase [34]. Another antioxidative enzyme is paraoxonase 1 (PON1) that has organophosphates, lactonase, and esterase activity and is located in high-density lipoproteins (HDL) [35]. Oxidative stress was also proposed as a modulator of hypoxia-inducible factor 1 (HIF1) activity [36, 37], a transcription factor involved in response to hypoxia that regulates the expression of several genes involved in important cell processes and diseases [38, 39].

There are significant differences in the occurrence of postirradiation toxicity among breast cancer patients, and genetic factors may contribute to the observed interindividual variability [40–42]. Several genetic polymorphisms affect the activity or expression of antioxidative enzymes [32, 39, 43–45] and could consequently also affect the occurrence of treatment-related cardiotoxicity.

The aim of our study was therefore to evaluate whether common polymorphisms in antioxidative genes affect the cardiotoxicity after adjuvant RT in HER2-positive early breast cancer patients.

2. Patients and Methods

2.1. Patients. Our retrospective study included patients with human epidermal growth factor receptor-2- (HER2-) positive left- or right-sided early breast cancer (stage I-III), treated concurrently with trastuzumab and RT at the Institute of Oncology Ljubljana between June 2005 and December 2010. HER2 status of the tumour was determined according to our standard clinical practice [8]. All patients were treated according to the clinical guidelines with surgery, chemotherapy, endocrine therapy in case of hormone receptor-positive disease, trastuzumab, and RT. Trastuzumab treatment started before RT or on the first day of RT at the latest. After

the adjuvant treatment with RT and trastuzumab, a follow-up clinical examination was performed. All patients also filled out questionnaires about smoking, concomitant diseases, and problems related to cardiovascular diseases. All other data were obtained from the patients' records.

The study was approved by the Republic of Slovenia National Medical Ethics Committee (approval number 39/05/15, 0120-54/2015-2) and was internationally registered at ClinicalTrial.gov (identifier NCT01572883). The study was conducted in accordance with the Declaration of Helsinki. All participants signed an informed consent before participating in the study.

2.1.1. Systemic Treatment. Data regarding systemic therapy were obtained from the patient's individual medical record. Most patients were treated with one of the chemotherapy regimens that include anthracyclines and taxanes and were used in standard clinical practice at the time of the treatment. Mostly used treatment schemes were as follows: Option 1: 4 cycles of epirubicin plus cyclophosphamide (EC) or doxorubicin plus cyclophosphamide (AC) every 3 weeks, followed by 12 cycles of paclitaxel weekly; Option 2: 4 cycles of EC or AC every 3 weeks, followed by 3 cycles of docetaxel every 3 weeks; or Option 3: 3 to 4 cycles of 5-fluorouracil, epirubicin, and cyclophosphamide (FEC) or doxorubicin in combination with 5-fluorouracil and cyclophosphamide (FAC) every 3 weeks, followed by 3-4 cycles of docetaxel every 3 weeks. The criteria for adjuvant treatment with trastuzumab regarding tumour, nodal stage, and cardiac function were the same as in pivotal adjuvant trials: tumours larger than 2 cm if node-negative disease, any tumour size if node-positive disease, WHO performance status zero or one, no serious concomitant cardiac disease, and treatment with adjuvant chemotherapy [46]. Treatment with trastuzumab started 3 weeks after the last cycle of anthracyclines and was prescribed for 1 year.

2.1.2. Locoregional Treatment. According to clinical guidelines patients were operated with either breast conservation surgery or mastectomy and either sentinel node biopsy or axillary dissection. After the operation and chemotherapy, they were irradiated using two-dimensional (2D RT) or three-dimensional conformal RT (3D CRT). Some of the patients received electron-beam chest wall irradiation. Whole breast RT was required in all patients who underwent breast cancer surgery. In addition to the irradiation of the breast/chest wall, all patients with 4 or more positive axillary lymph nodes also received regional RT.

Patients were irradiated with a total dose $(\mathrm{TD}) = 25 \times 2\,\mathrm{Gy}$, 5 fractions per week. A minority received RT with $\mathrm{TD} = 17 \text{ or } 18 \times 2.5\,\mathrm{Gy}$, 5 fractions per week. RT was performed 3 or more weeks after chemotherapy had been completed and concurrently with trastuzumab treatment as well as hormonal therapy in case of hormone receptor-positive breast cancer.

2.2. Assessment of Cardiotoxicity. Patients were classified according to New York Heart Association (NYHA) classification to assess signs of heart failure [47].

2.2.1. Echocardiography and Radionuclide Ventriculography. Echocardiography with LVEF measurement was performed before adjuvant RT and after the completed treatment with RT and trastuzumab. Baseline LVEF was determined either by using echocardiography or radionuclide ventriculography as previously described [8]. Normal range for LVEF was 50% or more. The difference between both LVEF measurements was analysed. Absolute change in LVEF was calculated as the difference between LVEF after completed adjuvant RT and trastuzumab treatment, and LVEF before RT. Important LVEF reduction was classified as a decrease of LVEF for ≥10% or a final value of LVEF <50% [17].

2.2.2. NT-proBNP. NT-proBNP was determined with the Cobas e 411 analyser (Roche) according to our standard clinical practice at the follow-up clinical examination after the adjuvant treatment with RT and trastuzumab [8]. According to the instructions of the manufacturer, the values of NT-proBNP below 125 ng/l exclude heart dysfunction [48].

2.3. DNA Extraction and Genotyping. Genomic DNA was extracted from buccal swabs (INFINITI Buccal Sample Collection Kit, AutoGenomics Inc., Vista, CA, USA) using QIAamp DNA Mini Kit (QIAGEN, Hilden, Germany) according to the manufacturer's instructions. Common putatively functional single nucleotide polymorphisms (SNPs) in antioxidative genes *GSTP1*, *CAT*, *SOD2*, *PON1*, and *HIF1* were selected based on literature search. Genotyping was performed using fluorescent-based competitive allele-specific polymerase chain reaction (KASP, LGC Genomics, UK) following the manufacturer's instructions.

2.4. Statistical Analysis. Continuous and categorical variables were described using median with interquartile range (25%–75%) and frequencies, respectively. A dominant genetic model was used in the analyses. Deviation from Hardy-Weinberg equilibrium (HWE) was evaluated using chi-square test, and SNPs not in HWE were excluded from further analyses. To evaluate the association of selected SNPs with markers of cardiotoxicity, univariable and multivariable logistic regression were used to calculate odds ratios (ORs) and 95% confidence intervals (CIs). Clinical parameters used for adjustment were selected using stepwise forward-conditional logistic regression. Fisher's exact test was used to compare genotype frequencies if there were no patients in one of the categories. The nonparametric Mann-Whitney test was used to compare the distribution of continuous variables. The statistical analyses were carried out by using IBM SPSS Statistics version 21.0 (IBM Corporation, Armonk, NY, USA). To determine the combined effect of more SNPs within one gene, we reconstructed haplotypes using Thesias with the most common haplotype serving as a reference [49]. All statistical tests were two-sided, and the level of significance was set at 0.05.

3. Results

We included 101 HER2-positive early breast cancer patients treated with adjuvant RT and trastuzumab. Regarding systemic treatment, 99 (98.0%) patients were also treated with

anthracyclines. Additionally, 58 (57.4%) received taxanes and 57 (56.4%) received hormonal therapy. Median time between the first and the last anthracycline application was 67 (51-105) days. Median time between the first and the last taxane application was 43 (42-75) days. Most patients (84, 83.2%) were irradiated with a total dose of 25 × 2 Gy, 5 fractions per week. All treatment was administered according to clinical guidelines. A total of 48 (47.5%) patients were operated and received RT on the left side. Detailed patients' characteristics and treatment parameters are presented in Table 1.

Median follow-up after diagnosis was 4.5 (3.2-5.9) years, and median follow-up after the onset of RT was 4.0 (2.6-5.4) years. Cardiotoxicity was evaluated in all patients after the treatment (Table 2). Median NT-proBNP level was 90 (56-157) ng/l. In total, 36 (35.6%) patients had increased NT-proBNP values with above 125 ng/l. Most patients did not exhibit signs of heart failure according to NYHA classification. After treatment, 17 (16.8%) patients had mild symptoms (NYHA class 2). LVEF measurements before and after RT were similar with the median change of 3 (-3 to 9) %. Important LVEF reduction was observed in 9 (8.9%) patients (Table 2).

All patients were genotyped for *PON1* rs854560 (p.Leu55Met), *PON1* rs662 (p.Gln192Arg), *GSTP1* rs1138272 (p.Ala114Val), *GSTP1* rs1695 (p.Ile105Val), *SOD2* rs4880 (p.Ala16Val), *CAT* rs1001179 (c.-330C>T), and *HIF1A* rs1154965 (p.Pro582Ser). Genotype and minor allele frequencies are presented in Supplementary Table 1. As *SOD2* rs4880 genotype distribution was not in agreement with HWE ($P = 0.004$), this SNP was excluded from further analyses. Genotype distributions of all other SNPs were in agreement with HWE.

3.1. NT-proBNP. Carriers of at least one polymorphic *PON1* rs854560 allele had significantly lower median NT-proBNP level ($P = 0.048$, Table 3, Figure 1(a)), while carriers of at least one polymorphic *PON1* rs662 allele had significantly higher median NT-proBNP level ($P = 0.007$, Table 3, Figure 1(b)).

Among clinical parameters, only higher age was significantly associated with increased NT-proBNP in our study group (OR = 0.61, 95% CI = 0.27-1.38, $P = 0.231$). Surgical treatment and RT side was not associated with increased NT-proBNP (right vs. left: OR = 1.05, 95% CI = 1.01-1.09, $P = 0.023$). None of the other treatment parameters, including chemotherapy parameters, or comorbidities were significantly associated with NT-proBNP (all $P > 0.05$).

Carriers of at least one polymorphic *PON1* rs854560 allele were significantly less likely to have increased NT-proBNP (OR = 0.34, 95% CI = 0.15-0.79, $P = 0.012$), even after adjustment for age (OR = 0.35, 95% CI = 0.15-0.83, $P = 0.017$) (Table 3). Carriers of at least one polymorphic *PON1* rs662 allele were significantly more likely to have increased NT-proBNP (OR = 4.44, 95% CI = 1.85-10.66, $P = 0.001$). This association remained significant even after adjustment for age (OR = 5.41, 95% CI = 2.12-13.78, $P < 0.001$). Additionally, carriers of at least one polymorphic *GSTP1* rs1695 were less likely to have increased NT-proBNP, but this difference was significant only after adjustment for age (OR = 0.36, 95% CI = 0.15-0.88, $P = 0.026$).

To evaluate the combined effect of both *PON1* SNPs on NT-proBNP, haplotype analysis was performed. Three haplotypes were observed in our study: *PON1* TA, AA in AG (SNP order from 5′-end to 3′-end: rs854560, rs662) and their estimated frequencies were 0.366, 0.366, and 0.267, respectively. Compared to reference *PON1* TA haplotype, carriers of *PON1* AG haplotype were significantly more likely to have increased NT-proBNP (OR = 5.48, 95% CI = 2.10-14.29, $P < 0.001$). On the other hand, *PON1* AA haplotype was not associated with NT-proBNP (OR = 1.33, 95% CI = 0.66-2.69, $P = 0.418$).

3.2. LVEF. Operation and RT side was not associated with LVEF reduction (right vs. left: OR = 1.15, 95% CI = 0.29-4.54, $P = 0.846$). Other clinical characteristics, including chemotherapy parameters, were also not associated with LVEF reduction in our study (all $P > 0.05$). None of the investigated SNPs was associated with LVEF (Table 4).

3.3. NYHA. Among clinical parameters, higher NYHA class was associated with higher body mass index (BMI) (OR = 1.20, 95% CI = 1.05-1.38, $P = 0.006$) and presence of hyperlipidemia (OR = 4.60, 95% CI = 1.39-15.19, $P = 0.012$). Operation and RT side was not associated with NYHA class (right vs. left: OR = 0.77, 95% CI = 0.27-2.19, $P = 0.624$). Other clinical characteristics, including chemotherapy parameters, were also not associated with NYHA class in our study (all $P > 0.05$).

Carriers of at least one polymorphic *CAT* rs1001179 allele were significantly more likely to be NYHA class 2 (OR = 4.09, 95% CI = 1.37-12.25, $P = 0.012$), even after adjustment for hyperlipidemia and BMI (OR = 4.14, 95% CI = 1.22-14.09, $P = 0.023$). Other SNPs were not associated with NYHA class in univariable or multivariable analysis (Table 4).

Among patients with left-sided breast cancer only, 9 (18.8%) patients were NYHA class 2. Carriers of at least one polymorphic *CAT* rs1001179 allele were still significantly more likely to be NYHA class 2 (OR = 5.09, 95% CI = 1.08-24.02, $P = 0.040$) in univariable analysis, while only a trend was observed after adjustment for hyperlipidemia and BMI (OR = 5.94, 95% CI = 0.84-42.22, $P = 0.075$). Other SNPs were also not associated with NYHA class in univariable or multivariable analysis in left-sided breast cancer (all $P > 0.05$).

4. Discussion

In the present study, we evaluated the association of genetic variability in antioxidative genes with cardiotoxicity in HER2-positive early breast cancer patients treated with adjuvant RT and trastuzumab. We showed that *PON1* rs854560 and rs662 as well as *GSTP1* rs1695 polymorphisms were associated with NT-proBNP levels, while *CAT* rs1001179 was associated with NYHA class.

Cardiotoxicity of breast cancer treatment has been widely investigated in recent years as improvements in cancer treatment that led to improved long-term survival also increased treatment-related cardiotoxicity [18]. Both systemic therapy

Table 1: Characteristics of breast cancer patients included in the study ($N = 101$) and treatment parameters.

Characteristic	Category/Unit	N (%)
Age	Years	50.9 (42.1-59.1)*
Type of surgery	Mastectomy	48 (47.5)
	Conservative surgery	53 (52.5)
Side of surgery	Left	48 (47.5)
	Right	53 (52.5)
Tumour type	Invasive lobular carcinoma	2 (2.0)
	Invasive ductal carcinoma	96 (95.0)
	Other	3 (3.0)
Cancer grade	1	1 (1.0)
	2	31 (30.7)
	3	69 (68.3)
Chemotherapy scheme	AC/EC/FAC/FEC with taxanes	54 (53.5)
	AC/EC/FAC/FEC without taxanes	43 (42.6)
	Other	4 (4.0)
Anthracyclines	Yes	99 (98.0)
	Doxorubicin	6 (6.0)
	Epirubicin	93 (92.1)
	No	2 (2.0)
Anthracyclines cumulative dose	Doxorubicin, mg/m^2 BSA	342 (318-413)*
	Epirubicin, mg/m^2 BSA	353 (294-522)*
Taxanes	Yes	58 (57.4)
	Paclitaxel	17 (16.7)
	Docetaxel	41 (40.6)
	No	43 (42.6)
Taxanes cumulative dose	Paclitaxel, mg/m^2 BSA	886 (739-938)*
	Docetaxel, mg/m^2 BSA	286 (269-299)*
Hormonal therapy	Yes	57 (56.4)
	No	44 (43.6)
Treatment scheme of RT	25 × 2 Gy	84 (83.2)
	17 or 18 × 2.5 Gy	17 (16.8)
Site of RT	Breast/mammary region	58 (57.4)
	(Breast/mammary region) + regional lymph nodes	43 (42.6)
RT technique	2D RT	80 (79.2)
	3D CRT	14 (13.9)
	Electrons	7 (6.9)
Hypertension	Yes	29 (28.7)
	No	72 (71.3)
Hyperlipidemia	Yes	21 (20.8)
	No	80 (79.2)
Smoking	Yes	16 (15.8)
	No	85 (84.2)
Diabetes	Yes	1 (1.0)
	No	100 (99.0)
Body mass index	kg/m^2	27.1 (24.3-29.7)*

*median (25%-75%). 2D RT: two-dimensional radiotherapy; 3D CRT: three-dimensional conformal radiotherapy; AC: doxorubicin, cyclophosphamide; BSA: body surface area calculated according to the Du Bois formula; EC: epirubicin, cyclophosphamide; FAC: 5-fluorouracil, doxorubicin, cyclophosphamide; FEC: 5-fluorouracil, epirubicin, and cyclophosphamide; Gy: Gray; RT: radiotherapy.

Table 2: Markers of cardiac side effects of breast cancer therapy.

Marker	Category/Unit	N (%)
Initial LVEF	%	65 (60-70)*
Absolute change in LVEF	%	3 (-3 do 9)*
LVEF reduction	No	92 (91.1)
	Yes	9 (8.9)
NT-proBNP	ng/l	90 (56-157)*
NT-proBNP	<125 ng/l	65 (64.4)
	≥125 ng/l	36 (35.6)
NYHA	Class 1	84 (83.2)
	Class 2	17 (16.8)

*median (25%-75%). LVEF: left ventricular ejection fraction; NT-proBNP: N-terminal pro B-type natriuretic peptide; NYHA: New York Heart Association. Absolute change in LVEF was calculated as the difference between LVEF after completed adjuvant radiotherapy and trastuzumab treatment, and LVEF before radiotherapy. LVEF reduction was classified as a decrease of LVEF for ≥10% or a final value of LVEF <50%.

and RT have been associated with increased risk of cardiac adverse events [18]. In our study, more than one third of patients exhibited signs of cardiotoxicity after treatment. Differences in systemic therapy or RT parameters among patients were not associated with any of the investigated cardiotoxicity parameters. Among other characteristics, the most important clinical predictor of increased NT-proBNP was higher age, which is consistent with other studies and is reflected also in reference ranges for healthy individuals [50]. BMI has been reported to be associated with NT-proBNP [50], but we did not observe any association with factors related to cardiovascular diseases such as BMI, smoking, hyperlipidemia or hypertension, or other clinical parameters. On the other hand, presence of hyperlipidemia and higher BMI were associated with mild symptoms of heart failure according to NYHA classification. Interestingly, none of the patients' or treatment characteristics were associated with important LVEF reduction.

Our results suggest that *PON1* genetic variability was the most important predictor of treatment-related cardiotoxicity in HER2-positive early breast cancer patients. The key observation was the association of *PON1* polymorphisms

Table 3: Association of polymorphisms in antioxidative genes with NT-proBNP levels.

SNP	Genotype	NT-proBNP median (25-75%)	P	NT-proBNP <125 ng/l, N (%)	NT-proBNP ≥125 ng/l, N (%)	OR (95% CI)	P	OR $(95\%\ CI)_{adj}$	P_{adj}
PON1	AA	126 (59-200)		21 (50.0)	21 (50.0)	Reference		Reference	
rs854560	AT+TT	79 (51-125)	**0.048**	44 (74.6)	15 (25.4)	0.34 (0.15-0.79)	**0.012**	0.35 (0.15-0.83)	**0.017**
PON1	AA	79 (47.75-118.5)		43 (79.6)	11 (20.4)	Reference		Reference	
rs662	AG+GG	135 (60-193)	**0.007**	22 (46.8)	25 (53.2)	4.44 (1.85-10.66)	**0.001**	5.41 (2.12-13.78)	**<0.001**
GSTP1	CC	92 (58-156)		53 (63.9)	30 (36.1)	Reference		Reference	
rs1138272	CT+TT	78.5 (36-165.5)	0.407	12 (66.7)	6 (33.3)	0.88 (0.30-2.56)	0.821	0.71 (0.23-2.16)	0.545
GSTP1	GG	122 (65.75-174.5)		24 (54.5)	20 (45.5)	Reference		Reference	
rs1695	GA+AA	77 (48.5-144)	0.101	41 (71.9)	16 (28.1)	0.47 (0.21-1.07)	0.073	0.36 (0.15-0.88)	**0.026**
CAT	GG	88 (52.5-148.25)		42 (65.6)	22 (34.4)	Reference		Reference	
rs1001179	GA+AA	96 (56-182)	0.680	23 (62.2)	14 (37.8)	1.16 (0.50-2.70)	0.762	0.99 (0.41-2.36)	0.973
HIF1A	CC	91 (56-154.5)		56 (63.6)	32 (36.4)	Reference		Reference	
rs1154965	CT+TT	79 (54.5-180)	0.666	9 (69.2)	4 (30.8)	0.78 (0.22-2.73)	0.695	0.87 (0.24-3.13)	0.827

Adj: adjusted for age; CI: confidence interval; NT-proBNP: N-terminal pro B-type natriuretic peptide; OR: odds ratio.

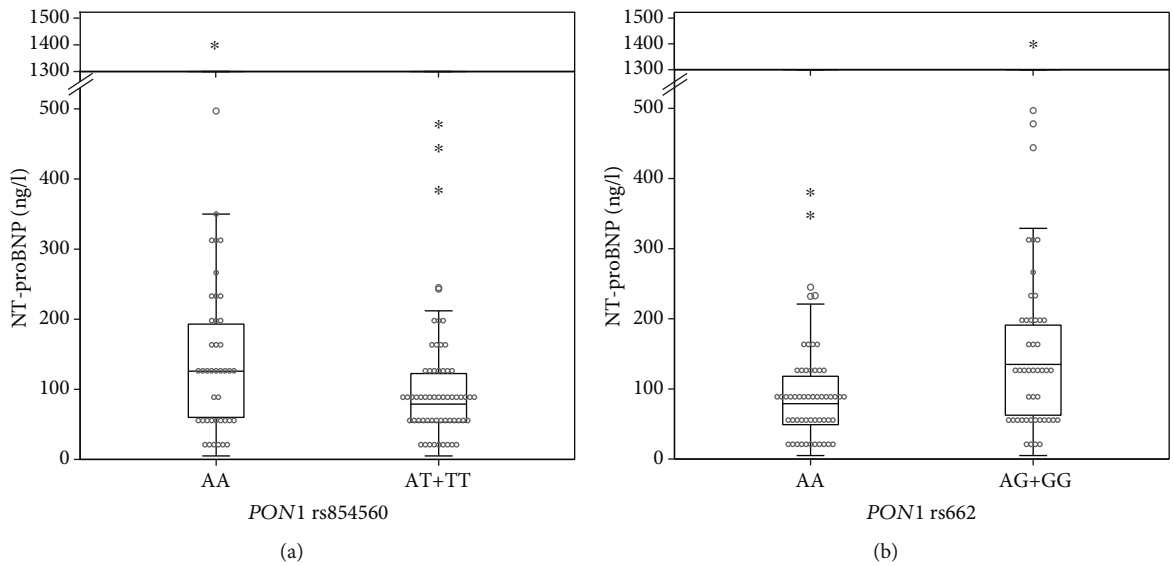

Figure 1: The association of *PON1* rs854560 (a) and *PON1* rs662 (b) polymorphisms with N-terminal pro B-type natriuretic peptide (NT-proBNP) levels after adjuvant radiotherapy in HER2-positive breast cancer patients.

with NT-proBNP: polymorphic *PON1* rs854560 T allele was associated with lower NT-proBNP levels, while *PON1* polymorphic rs662 G allele was associated with higher NT-proBNP levels. Additionally, an even larger association with increased NT-proBNP was observed in *PON1* AG haplotype combining both normal rs854560 and polymorphic rs662 allele associated with higher NT-proBNP in single SNP analysis.

PON1 is a plasma enzyme located in HDL that has antioxidative, antiatherosclerotic, and anti-inflammatory role [51]. PON1 inhibits LDL oxidation, prevents accumulation of oxidized LDL, and stimulates cholesterol efflux from macrophages [51, 52]. PON1 activity is inversely correlated with cardiovascular diseases [45, 51, 52]. Several functional polymorphisms were identified in the *PON1* gene. *PON1* rs854560 is a nonsynonymous SNP, and the leucine to methionine substitution was previously associated with increased enzyme activity and serum concentration [45, 53, 54]. *PON1* rs662 is also a nonsynonymous SNP, leading to a glutamine to arginine substitution with the biggest impact on enzyme activity [53]. Polymorphic rs662 G allele results in lower enzymatic activity that limits PON1 capacity for lipid peroxide hydrolysis and therefore less effectively inhibits LDL oxidation [45, 54]. Interestingly, rs662 has been associated with a substrate-specific change in enzyme activity: the polymorphic allele was associated with increased paraoxonase activity, while hydrolytic activity towards other substrates was lower [45, 53, 55]. *PON1* rs662 was also associated with increased LDL and decreased HDL concentrations [56, 57]. The association of *PON1* rs854560 with lipoprotein levels is less pronounced and might also vary in different pathologies [51]. This data is in concordance with

Table 4: Association of polymorphisms in antioxidative genes with NYHA class and LVEF reduction.

SNP	Genotype	NYHA						LVEF reduction			
		Class 1, *N* (%)	Class 2, *N* (%)	OR (95% CI)	*P*	OR (95% CI)$_{adj}$	P_{adj}	No, *N* (%)	Yes, *N* (%)	OR (95% CI)	*P*
PON1 rs854560	AA	33 (78.6)	9 (21.4)	Reference				38 (90.5)	4 (9.5)	Reference	
	AT+TT	51 (86.4)	8 (13.6)	0.58 (0.20-1.64)	0.301	0.61 (0.19-1.99)	0.416	54 (91.5)	5 (8.5)	0.88 (0.22-3.49)	0.885
PON1 rs662	AA	44 (81.5)	10 (18.5)	Reference				50 (92.6)	4 (7.4)	Reference	
	AG+GG	40 (85.1)	7 (14.9)	0.77 (0.27-2.22)	0.628	0.88 (0.27-2.84)	0.832	42 (89.4)	5 (10.6)	1.49 (0.38-5.90)	0.572
GSTP1 rs1138272	CC	69 (83.1)	14 (16.9)	Reference				75 (90.4)	8 (9.6)	Reference	
	CT+TT	15 (83.3)	3 (16.7)	0.99 (0.25-3.87)	0.984	0.88 (0.20-3.92)	0.862	17 (94.4)	1 (5.6)	0.55 (0.07-4.71)	0.586
GSTP1 rs1695	GG	36 (81.8)	8 (18.2)	Reference				38 (86.4)	6 (13.6)	Reference	
	GA+AA	48 (84.2)	9 (15.8)	0.84 (0.30-2.40)	0.750	0.84 (0.26-2.74)	0.773	54 (94.7)	3 (5.3)	0.35 (0.08-1.50)	0.157
CAT rs1001179	GG	58 (90.6)	6 (9.4)	Reference				58 (90.6)	6 (9.4)	Reference	
	GA+AA	26 (70.3)	11 (29.7)	4.09 (1.37-12.25)	**0.012**	4.14 (1.22-14.09)	**0.023**	34 (91.9)	3 (8.1)	0.85 (0.20-3.63)	0.830
HIF1A rs1154965	CC	71 (80.7)	17 (19.3)	Reference				81 (92.0)	7 (8.0)	Reference	
	CT+TT	13 (100.0)	0 (0.0)	/	0.118*			11 (84.6)	2 (15.4)	2.10 (0.39-11.44)	0.389

Adj: adjusted for hyperlipidemia and body mass index. *calculated using Fisher's exact test. CI: confidence interval; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; OR: odds ratio.

our results, as the polymorphic rs854560 T allele, associated with higher enzyme activity, was also associated with lower cardiotoxicity, while the polymorphic rs662 G allele, associated with lower enzyme activity, was associated with increased cardiotoxicity in our study.

A lot of studies also investigated the influence of *PON1* polymorphisms on the risk of developing different cardiovascular diseases. Generally, *PON1* rs662 was associated with slightly increased cardiovascular disease risk, especially in the recessive genetic model, while *PON1* rs854560 was associated with somewhat decreased risk in meta-analyses [58–62], consistent with our results. However, some studies found no significant associations and differences were observed among different populations [58, 59]. On the other hand, several studies also investigated the role of *PON1* polymorphisms in cancer risk. Despite discrepancies among different studies, latest meta-analyses suggest rs662 is associated with lower breast cancer risk, while rs854560 is associated with increased breast cancer risk [63–66]. These results also suggest rs662 and rs854560 have an opposite effect, but further studies are needed as different results were observed in other cancer types [65].

Studies suggest serum PON1 level and its activity are lower in cancer patients, including breast cancer [67–70], but only a few studies investigated the role of PON1 in cancer treatment response or toxicity. So far, no studies investigated the association of PON1 with response to trastuzumab or anthracyclines, while a few studies focusing on RT were already published [55, 69, 70]. In breast cancer patients treated with adjuvant RT, PON1 concentration and activity increased after RT with significant differences observed among different molecular subtypes [70]. In luminal B (HER2-positive) subtype, PON1 concentration after RT was lower compared to luminal A subtype. HER2 expression was also associated with altered expression of other antioxidative enzymes, which could modify the risk for cardiotoxicity [70, 71]. In lung cancer, as well as head and neck cancer patients treated with RT, PON1 concentration also increased after RT [69]. Additionally, in patients with nasopharyngeal carcinoma, the combination of *PON1* rs662 and another polymorphism, rs705379 (c.-108C>T) was associated with carotid atherosclerosis after RT of the neck, while *PON1* rs854560 was not investigated [55]. In contrast to other studies, rs662 was associated with lower carotid plaque scores, which could be partly due to differences in activities observed for different substrates [55]. Better evaluation of *PON1* genetic variability, concentration or activity is therefore needed to improve the understanding of PON1 role in cardiovascular disease and especially in treatment-related cardiotoxicity.

In our study, polymorphic *GSTP1* rs1695 A allele was also significantly associated with lower risk for increased NT-proBNP after accounting for age. GSTP1 is involved in detoxification of xenobiotics through conjugation with glutathione [72]. *GSTP1* rs1695 is a nonsynonymous SNP that leads to lower enzyme activity [73]. Several studies investigated the role of *GSTP1* rs1695 in breast cancer susceptibility or response to treatment [73–79]. Latest meta-analyses suggest this SNP might contribute to increased breast cancer risk; however, the association was significant only in specific populations [73, 76, 77]. *GSTP1* polymorphisms with lower enzyme activity were also proposed to be associated with better treatment outcome [78, 79], and based on meta-analysis results, *GSTP1* rs1695 could serve as a predictor of response to anthracycline-based chemotherapy [78]. Additionally, this could also lead to altered risk of treatment-related toxicity. In a previous study, *GSTP1* rs1695 was not associated with LVEF reduction after treatment with anthracyclines, consistent with our results, while NT-proBNP was not evaluated [80]. No studies investigated the association of *GSTP1* with cardiotoxicity of treatment with RT or trastuzumab. However, rs1695 was previously associated with increased heart failure and coronary artery disease risk [81, 82]. Apart from its role in response to oxidative stress and lipid peroxidation, GSTP1 may also affect different signalling pathways, which could contribute to the observed association with heart disease [81]. Additional studies are needed to better understand the role of GSPT1 and its potential interaction with other clinical parameters in cardiotoxicity of breast cancer treatment, especially in patients treated with RT.

Carriers of at least one polymorphic *CAT* rs1001179 A allele were significantly more likely to exhibit mild symptoms of heart failure according to NYHA classification in our study, even after taking into account hyperlipidemia and BMI. This association was also observed in univariable analysis in the subgroup of left-sided breast cancer patients. In these cases, the heart lies directly below the target tissue for irradiation. *CAT* rs1001179 is located in the promoter region of the gene and was previously associated with lower expression and activity of catalase and thus could confer worse defence against oxidative stress [43, 83]. Overall, the role of *CAT* genetic variability in breast cancer is not well known, with previous studies suggesting rs1001179 is not associated with breast cancer risk [84]. Only a handful of studies have previously investigated the role of *CAT* genetic variability in cardiotoxicity of anthracyclines, while so far, no study has investigated cardiotoxicity of treatment with RT or trastuzumab [85–87]. In one study, intronic SNP *CAT* rs10836235 was associated with cardiac damage in childhood acute leukemia patients treated with anthracyclines, but no significant association with *CAT* rs1001179 was observed [85]. GWAS and meta-analyses did not identify catalase as a risk factor for cardiotoxicity of anthracyclines [86, 87]. Studies investigating the role of *CAT* polymorphisms in cardiovascular disease are also scarce; however, *CAT* rs1001179 was not a risk factor for coronary artery disease in a recent study [88]. Further studies are therefore needed to elucidate the role of catalase in the development of cardiotoxicity of breast cancer treatment after different treatment modalities.

The main limitation of our study was its small sample size. However, we had clear inclusion and exclusion criteria and thus included a clinically well-defined study group of patients with a HER2-positive breast cancer subtype with thorough evaluation of cardiotoxicity parameters. According to the available literature, we were the first to evaluate the role of genetic variability in cardiotoxicity after adjuvant RT in HER2-positive breast cancer patients. Another limitation of our study is the fact that we had to exclude *SOD2* rs4880 from

the analysis as it was not in agreement with HWE. As *SOD2* rs4880 was marginally associated with breast cancer risk in Caucasians, this could contribute to the observed deviation from HWE [89]. Still, we were among the first to assess the influence of genetic variability of several antioxidative genes on cardiotoxicity of breast cancer treatment and the first to show that especially *PON1* polymorphisms could contribute to the occurrence of cardiac adverse events. As our patients were treated with different treatment modalities that all contribute to cardiotoxicity, studies on patients treated only with RT or with only one type of systemic therapy could help elucidate the role of the investigated polymorphisms. Larger studies are therefore needed to further validate our results.

5. Conclusions

In conclusion, our study indicates that functional polymorphisms in antioxidative genes might serve as biomarkers of treatment-related cardiotoxicity in breast cancer patients. Better understanding of adverse events could improve patient management and affect the health and quality of life of breast cancer patients. In the future, genetic markers could contribute to the personalization of RT and systemic therapy in breast cancer patients.

Data Availability

The data used to support the findings of this study are included within the article and supplementary information file.

Conflicts of Interest

The authors declare no conflict of interest.

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Supplementary Materials

Supplementary Table 1: genotype frequencies of investigated polymorphisms. *(Supplementary Materials)*

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