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Research Article

Adjuvant Therapy Using Dabrafenib plus Trametinib in Chinese Patients with Resected Stage III Melanoma: A Multicenter Retrospective Cohort Study

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Background. In patients with stage III melanoma carrying BRAF mutations, the risk of melanoma recurrence is relatively high even after complete resection of the primary melanoma and regional lymph nodes. *Methods*. We collected data from patients with stage III cutaneous and acral melanoma who received adjuvant trametinib combined with dabrafenib from three cancer centres in China between August 2019 and December 2022. *Results*. A total of 55 patients were included in this study. The one-year recurrence-free survival (RFS) rate was 79.8% (95% CI 73.6–86.0%). The one-year RFS rate was 79.8% (95% CI 72.8–86.8%) in the cutaneous melanoma subgroup, while the one-year RFS rate was 74.1% (95% CI 58.0–90.2%) in the acral melanoma subgroup. Six (46.2%) patients experienced recurrence during adjuvant therapy; 7 (53.9%) patients recurred after completion of the regimen. At the time of the first recurrence, distant metastasis occurred in 10 patients, local recurrence occurred in 2 patients, and one patient experienced both distant metastasis and local recurrence. *Conclusions*. This study confirmed the good tolerability and short-term benefits of adjuvant therapy with dabrafenib and trametinib in Chinese patients with stage III melanoma with BRAF V600 mutation.

1. Introduction

Malignant melanoma is a highly lethal skin malignancy that has a significant increase in incidence in both Caucasians and Asians in recent decades. Mortality rates have increased more rapidly in Chinese populations compared to Caucasians [1]. Although the incidence of malignant melanoma remains low in China, approximately 20,000 new cases are reported annually [2]. Lymph node metastasis is highly susceptible in malignant melanoma, and 25.1% of Chinese patients with malignant melanoma are found to have lymph node metastasis at the initial diagnosis.

BRAF is a serine/threonine protein kinase encoded on chromosome 7q34 that activates the MAPK/ERK signaling pathway and is activated by Ras [3, 4]. Previous studies have found that BRAF mutations occur in approximately 40–55% of melanoma patients [5, 6]. Professor Guo Jun's team conducted genetic testing of 432 Chinese patients with primary melanoma and found that the BRAF mutation rate was 25.9%. Among them, the mutation rates of acral and cutaneous BRAF were 17.9% and 50%, respectively, with V600E being the most common mutation site (87.6%) [7].

Insights into melanoma gene mutations have led to the development of specific small molecule inhibitors targeting mutant BRAF proteins. Two independent phase 3 clinical trials (COMBI-d and COMBI-v) demonstrated that treatment with the BRAF inhibitor dabrafenib in combination with the MEK inhibitor trametinib improved overall survival in patients with unresectable or metastatic melanoma with BRAF mutations [8, 9]. A clinical trial conducted in East

Asia demonstrated significant efficacy of dabrafenib in combination with trametinib in East Asian patients with advanced malignant melanoma [10].

In patients with stage III melanoma with regional lymph node metastases, the risk of melanoma recurrence is relatively high even after complete resection of the primary melanoma and regional lymph nodes. The combination of dabrafenib in combination with trametinib has shown clinical benefits in melanoma patients at a high risk of recurrence, leading to FDA approval of targeted agents as adjuvant therapy. Japanese scholars have validated the efficacy and safety of dabrafenib combined with trametinib as adjuvant therapy in Japanese patients with melanoma in a real-world study [11].

In this study, we retrospectively analyzed the efficacy and safety of dabrafenib combined with trametinib as adjuvant therapy in 55 Chinese patients from three centres with stage III malignant melanoma carrying BRAF mutations.

2. Methods

2.1. Patients. We collected data from patients with stage III cutaneous and acral melanoma who received adjuvant trametinib combined with dabrafenib from three cancer centres in China between August 2019 and December 2022. The patients had to be confirmed stage III cutaneous or acral melanoma that was positive for a $BRAF^{V600E}$ or $BRAF^{V600K}$ mutation. Complete resection of the primary tumor and metastatic disease, as well as regional lymph node dissection if lymph nodes were involved, was required to have been performed within 13 weeks before the start of adjuvant treatment with trametinib combined with dabrafenib. The exclusion criteria included the use of systemic treatment or radiotherapy against melanoma, clinical or imaging evidence of residual tumor after surgery, or having been diagnosed with malignancies other than melanoma.

2.2. Treatment Schedule. Patients were administered dabrafenib (150 mg twice daily) and trametinib (2 mg once daily) for 12 months or until disease recurrence or unacceptable toxicity. Physicians could adjust the dose or interrupt treatment if patients experienced grade 2 or higher nonhematologic adverse events that did not resolve with conventional management.

2.3. Primary and Secondary End Points. The primary endpoint of this study was the one-year relapse-free survival (RFS) rate, defined as the time from the initial time of adjuvant therapy to disease recurrence or death from any cause. Safety assessment included the collection of adverse events' data, clinical laboratory tests, physical examination results, and vital signs. The severity class of each adverse reaction and the relationship to the drug were determined by reference to the Common Terminology Criteria for Adverse Events (CTCAE).

2.4. Statistical Analysis. We described the measures using the mean ± standard deviation or median (interquartile range) and counts using n (%). We assessed RFS rates using Kaplan–Meier curves and performed statistical analyses using SPSS version 24.0 for Windows (IBM Corporation, Armonk, NY, USA).

3. Results

3.1. Demographic Data of Patients. A total of 55 patients were included in this study, with patient demographics presented in Table 1. Of these patients, 47.3% ($n = 26$) were from Zhejiang Cancer Hospital, with the remainder from the Fudan University Shanghai Cancer Center ($n = 25$, 45.5%) or Tianjin Cancer Hospital ($n = 4$, 7.3%). Of the 55 patients, 19 were male and 36 were female, with a median age of 53 years (range 27–82 years). 41 patients (74.5%) had cutaneous acral melanoma, and 12 patients (21.8%) had acral melanoma, with 2 (3.6%) having no identifiable skin lesion. All patients carried BRAF V600E (51 cases) or BRAF V600K mutations (4 cases). Among the 55 patients, 3 (5.5%) had melanoma stage IIIA, 7 (20%) had melanoma stage IIIB, 27 (49.1%) had stage IIIC, 7 (12.7%) had stage IIID, and 7 (12.7%) had stage III (exact stage unknown). 32 patients had ulcers, 19 had no ulcers, and 4 had an unknown status. As of December 31, 2022, the median follow-up time was 26 months (range 5–45 months).

3.2. Efficacy Assessment. As of December 31, 2022, 30 patients (54.5%) had completed one year of adjuvant therapy. Tumor recurrence was reported in 13 (23.6%) of all 55 patients. The one-year recurrence-free survival (RFS) rate was 79.8% (95% CI 73.6–86.0%, Figure 1). The one-year RFS rate was 79.8% (95% CI 72.8–86.8%) in the cutaneous melanoma subgroup, while the one-year RFS rate was 74.1% (95% CI 58.0–90.2%) in the acral melanoma subgroup. There was no significant difference in RFS between the cutaneous melanoma subgroup and the acral melanoma subgroup (Figure 2, log-rank $p = 0.55$). Six (46.2%) patients experienced recurrence during adjuvant therapy; 7 (53.9%) patients recurred after completion of the regimen. At the time of the first recurrence, distant metastasis occurred in 10 patients, local recurrence occurred in 2 patients, and one patient experienced both distant metastasis and local recurrence.

3.3. Safety Assessment. Of the 55 patients, 38 (69.1%) reported at least one adverse event, with 17 patients (30.9%) experiencing grade 3 or 4 serious adverse reactions. The most common adverse reactions were fever, fatigue, and nausea, as shown in Table 2. Panniculitis occurred in 8 patients, mainly involving the thighs and upper extremities (Figure 3). One patient (1.8%) had permanent discontinuation of the drug due to an adverse event, 11 patients (20%) had dose adjustment due to an adverse event, and 10 patients (18.2%) discontinued the drug due to an adverse event.

Table 1: Baseline characteristics.

Characteristics	Combination therapy group ($n = 55$)
Patient origin no. (%)	
Zhejiang	26 (47.3)
Shanghai	25 (45.5)
Tianjin	4 (7.3)
Median age, years	53 (27–82)
Sex	
Male	19 (34.5%)
Female	36 (65.5%)
Histology	
Cutaneous	41 (74.5%)
Acral	12 (21.8%)
Unknown	2 (3.6%)
Stage	
IIIA	3 (5.5%)
IIIB	11 (20%)
IIIC	27 (49.1%)
IIID	7 (12.7%)
III unspecified	7 (12.7%)
Primary tumor ulceration	
Yes	32 (58.2%)
No	19 (34.5%)
Unknown	4 (7.3%)
BRAF status	
V600E	51 (92.7%)
V600K	4 (7.3%)

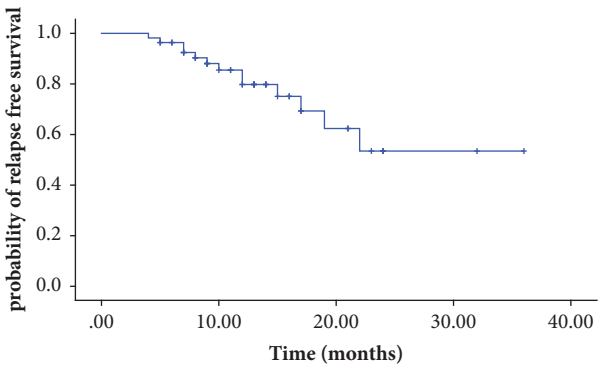

Figure 1: Kaplan–Meier curves of relapse-free survival melanoma patients treated with adjuvant dabrafenib plus trametinib.

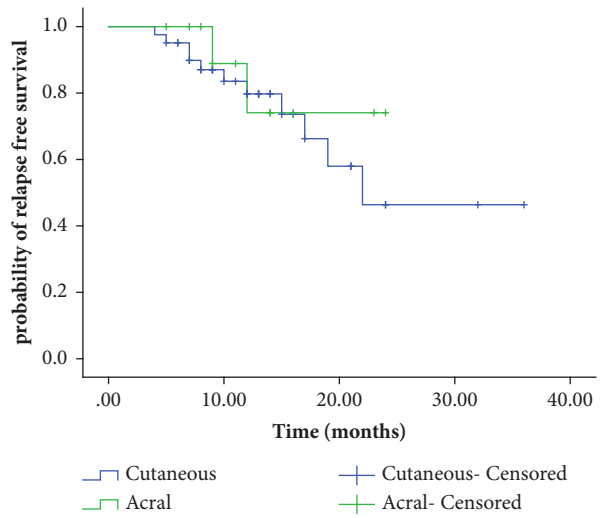

Figure 2: Relapse-free survival for melanoma patients stratified by the cutaneous subgroup versus the acral subgroup (log-rank $p = 0.55$).

Table 2: Safety profile of adjuvant dabrafenib plus trametinib.

Adverse event	Any grade	Grade 3 or 4
Any adverse event	38 (69.1%)	17 (30.9%)
Pyrexia	31 (56.4%)	13 (23.6%)
Fatigue	17 (30.9%)	4 (7.3%)
Nausea	15 (27.3%)	3 (5.5%)
Headache	14 (25.5%)	3 (5.5%)
Chills	12 (21.8%)	2 (3.6%)
Diarrhea	11 (20%)	2 (3.6%)
Rash	10 (18.2%)	1 (1.8%)
Vomiting	9 (16.4%)	1 (1.8%)
Arthralgia	8 (14.5%)	0
Panniculitis	8 (14.5%)	0
Cough	8 (14.5%)	0
Elevated alanine aminotransferase	7 (12.7%)	0
Elevated aspartate aminotransferase	6 (10.9%)	0
Peripheral edema	5 (9.1%)	0
Constipation	5 (9.1%)	0
Hypertension	2 (3.6%)	0
Decreased appetite	1 (1.8%)	0
Erythema	1 (1.8%)	0

4. Discussion

This study included 55 patients over three years, reflecting the relatively low incidence of melanoma in China, with national statistics estimating about 20,000 new cases annually [1]. The prevalence of the BRAF V600 mutation is lower in the Chinese population (approximately 25.9%) compared to up to 50–60% in Western countries [7]. Additionally, the recent COVID-19 pandemic likely impacted patient recruitment and follow-up due to healthcare disruptions, although this effect was not directly measured in our study.

In our study, acral melanoma, which is predominant in Asian populations, accounted for 21.8% of cases, less than expected. This finding aligns with Professor Guo Jun's genetic analysis of 432 Chinese melanoma patients, showing a BRAF mutation rate of 25.9% overall, with lower rates in acral melanoma (17.9%) compared to cutaneous melanoma (50%) [7]. Acral melanomas generally lack UV signature mutations and display complex chromosomal variations [12]. Additionally, acral melanomas are often diagnosed at later stages due to their less noticeable clinical presentation, potentially leading to advanced disease at diagnosis and exclusion from studies like ours.

In a phase III clinical trial (COMBI-AD), the combination of dabrafenib and trametinib was administered as adjuvant therapy in patients with melanoma having BRAF V600E or V600K mutations. In the group of patients receiving targeted adjuvant therapy, the 1-year relapse-free survival rate was 88%, while the 1-year overall survival rate

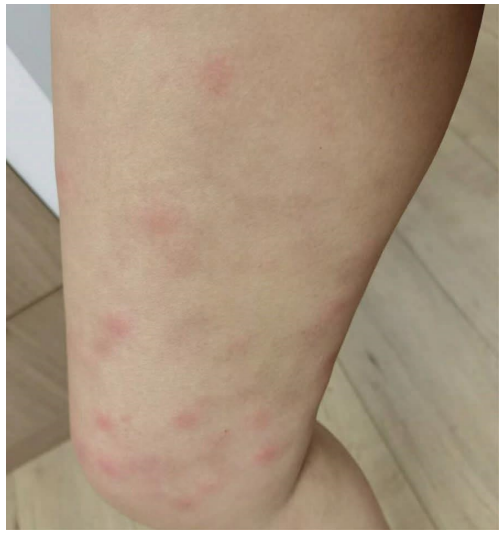

Figure 3: Clinical presentation of the panniculitis in one patient.

was 97% [13]. Upon 5 years of follow-up, the median recurrence-free survival (RFS) rate in the dabrafenib and trametinib combination therapy group had not yet been reached, and the 5-year recurrence-free survival rate was 52%, while the 5-year distant metastasis-free survival rate was 65% [14]. In a retrospective analysis conducted by Japanese scholars, the efficacy and safety of adjuvant therapy with dabrafenib plus trametinib were assessed in 36 Japanese melanoma patients [11]. They reported that the 1-year recurrence-free rate was 82.1% in the overall population. In our present study, the 1-year RFS rate was 79.8% (95% CI 73.6–86.0%) in the total cohort. The one-year RFS rate was 79.8% (95% CI 72.8–86.8%) in the cutaneous subgroup, and the one-year RFS rate was 74.1% (95% CI 58-90.2%) in the acral subgroup.

Despite acral melanoma being the most common subtype of melanoma in Asians, the enrolled cases in both China and Japan mostly included cutaneous melanoma cases, which accounted for more than 70% of the cases. This was due to the higher BRAF mutation rate observed in cutaneous melanoma than in acral melanoma. The 1-year RFS rate in the present study was similar to that observed in Japanese patients, and both were lower than that observed in Caucasians. This could be due to more earlier stage patients included in COMBI-AD, with 58% of patients with IIIA and IIIB included in COMBI-AD, as opposed to less than 30% in both our and Japanese studies.

In the Caucasian population, the PD-1 monoclonal antibody has shown significant clinical benefits as adjuvant therapy for patients with stage III resectable melanoma [15]. Indirect comparisons of clinical trials with different baseline characteristics have shown that the incidence of early resistance to adjuvant therapy with dabrafenib plus trametinib appeared to be lower than that of PD-1 monoclonal antibody. However, the proportion of patients being surviving and free of recurrence was almost similar between the two regimens after 24 months of follow-up [13]. A previous study conducted by our team found the 6-month RFS rate of 77.7% in the adjuvant group of pembrolizumab for stage III cutaneous and acral melanoma in Chinese [16]. A study by Sun Yat-sen University found that the 1-year RFS rate was 77.8% in the adjuvant anti-PD-1 monotherapy group for stage III cutaneous melanoma and 50% for acral melanoma in Chinese [17]. The KEYNOTE-054 clinical trial found that the 1-year RFS rate was 75.4% in the adjuvant pembrolizumab group for stage III cutaneous melanoma in the Caucasian population [15]. In the present study, the 1-year RFS rate in the cutaneous subgroup was 79.8%, slightly higher than the result in the adjuvant anti-PD-1 monoclonal antibody group from previous studies. As adjuvant therapy for malignant melanoma, dabrafenib plus trametinib appears to have an early advantage over PD-1 monoclonal antibodies, but this conclusion needs to be interpreted with caution as the comparison is based on different study baselines.

Acral melanoma is known to be highly resistant to immunotherapy [18, 19]. However, a clinical trial conducted on Chinese patients with advanced melanoma revealed that the combination therapy of dabrafenib and trametinib had 83.3% of ORR in the acral melanoma subgroup and 70.8% of ORR in the nonacral melanoma subgroup. Although the median PFS and overall survival (OS) rates were slightly lower in the acral subgroup as compared to nonacral patients, the 3-year PFS and OS rates in acral melanoma patients were similar to those observed in cutaneous melanoma cases [20]. Notably, one-year RFS rate was 74.1% (95% CI 58-90.2%) in the acral subgroup, which is better than the previous result from the adjuvant anti-PD-1 monoclonal antibody group.

In the COMBI-AD trial, the first relapse occurred in 12% of patients with local recurrence, 2% with local and distant recurrence, and 22% with distant recurrence. Studies conducted by our team indicate that the first recurrence after the failure of adjuvant immunotherapy for malignant melanoma was local only in 41%, distant in 47.5%, and both local and distant in 11.5% of cases [21]. In this study, distant metastasis occurred in 10 patients, while local recurrence occurred in 2 patients, and both local and distant recurrence occurred in one patient. These findings suggest that patients are more likely to develop distant metastases after the failure of adjuvant targeted therapy as compared to adjuvant immunotherapy.

In the COMBI-AD trial, 97% of patients reported experiencing at least one adverse event, and 26% of them had to discontinue the treatment permanently due to these events. Additionally, 38% of the patients had to undergo dose reductions, and 66% had to interrupt their doses due to adverse events. A retrospective analysis conducted by Japanese scholars found that the incidence of any adverse events was 69.7% among all patients, with fever and rash being the most common adverse events. In the present study, 38 patients (69.1%) reported at least one adverse event, and the most frequently reported adverse events associated with the combination therapy were fever, fatigue, and nausea, which were consistent with those observed in previous trials. However, fewer patients in this study had to discontinue the

treatment permanently, undergo dose reductions, or interrupt their doses due to adverse events, and almost all adverse events associated with dabrafenib in combination with trametinib were transient and resolved after the interruption of therapy.

Notably, panniculitis was observed in 8 (14.5%) female patients in this study, primarily affecting the thighs and upper limbs. A retrospective analysis by Professor Francesca Consoli of 52 patients with advanced melanoma treated with dabrafenib and trametinib reported a 15.4% incidence of panniculitis, with all cases involving the thighs, and three also involving the upper limbs [22]. Panniculitis is believed to be a manifestation of immune system activation in vivo and may be associated with higher response rates to BRAF and MEK inhibitors in advanced melanoma. In the present study, only one of the eight patients who developed panniculitis experienced a local recurrence after 12 months of drug administration. The patients with panniculitis may benefit more from adjuvant targeted therapy, but further investigation with larger samples is necessary to establish this link.

Our study provides critical insights into the efficacy and safety of adjuvant therapy with dabrafenib and trametinib among a predominantly Chinese cohort, emphasizing the unique demographic and genetic characteristics of Asian populations compared to Western counterparts. These data are essential for enhancing the global understanding of melanoma treatment outcomes across diverse genetic and environmental contexts.

This study had some obvious limitations. Firstly, the sample size was small, which limited the ability to analyze subgroups. Secondly, no control group was established for direct comparison. Thirdly, the follow-up period was brief, and only short-term benefits could be evaluated.

In summary, this study confirmed the good tolerability and short-term benefits of adjuvant therapy with dabrafenib and trametinib in Chinese patients with stage III melanoma with BRAF V600 mutation.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent

Informed consent was obtained from all individual participants included in the study.

Conflicts of Interest

All authors declare that they have no conflicts of interest.

Authors' Contributions

All authors contributed to the study conception and design. Data collection and analysis were performed by Dong-Dong Jia, Yu Xu, and Ting Li. Ji-Long Yang, Yong Chen, and Tao Li were major contributors in writing the manuscript. All authors read and approved the final version of the manuscript. The authors Dong-Dong Jia, Yu Xu, and Ting Li contributed equally.

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