Cyclophosphamide: An alternative treatment in Crohn’s disease

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ABSTRACT: Immunosuppressive therapy in the form of 6-mercaptopurine has shown a 66% efficacy in severe, debilitating, highly corticosteroid dependent Crohn’s disease. Nevertheless this medication has some important side effects such as nausea, vomiting, leukopenia and pancreatitis. Two patients are presented who, suffering from severe Crohn’s disease, were unable to tolerate 6-mercaptopurine but showed an amazing improvement with cyclophosphamide.

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CASE ONE

A 34-year-old woman had a cholecystectomy, an appendectomy and a laparotomy for post cholecystectomy hemorrhage prior to 1978. Her mother died from Crohn’s disease at the age of 38. In 1978 Crohn’s disease was diagnosed in-
volving the terminal ileum to the proximal sigmoid; rectosigmoidoscopy was normal to 25 cm. The patient was treated conventionally with corticosteroids and salicylazosulfapyridine.

In 1981, because of conjunctivitis, arthritis, significant gastrointestinal hemorrhage, poor health and treatment resistance, the patient was submitted to a subtotal colectomy and permanent ileostomy. A few months later, laparotomy was required for small bowel obstruction due to adhesions, and an abdomino-perineal resection was subsequently performed. Pathological reports were consistent with ulcerative colitis (pathognomonic ulcer type and lack of granulomata).

In March 1985, she experienced a recurrence of Crohn's disease. The patient had pain, bloating, fever, chills, nausea, vomiting, weakness and a 35 lb (16 kg) weight loss. On physical examination she was pale and had muscular atrophy. A few ileal segments showed edema, ulcers and pre-ileostomy rigidity on upper gastrointestinal series. White blood count was 17,000/mm³, with 84% polymorphonuclear leukocytes. Erythrocyte sedimentation rate was 24 mm/h and proteins 53 g/L. She was treated with corticotherapy and total parenteral nutrition and went into remission. The remission on cortisone lasted about six months. The patient was rehospitalized in April 1986 in the same poor condition with corticosteroid side effects.

Upper gastrointestinal series and endoscopy depicted disease involving the ileum, the mucosa being friable, edematous and ulcerated.

The patient was again started on total parenteral nutrition and corticotherapy; 6-mercaptopurine 50 mg daily was also prescribed. Fifteen days later, she returned to hospital because of pancreatitis. Serum amylase was 423 Somogyi units/dL, which returned to normal upon the withdrawal of 6-mercaptopurine. After discharge, because of the difficulty of differentiating pancreatitis from sub-occlusion, 6-mercaptopurine was re-started. Five days later the patient was readmitted with a recurrent pancreatitis.

In July 1987, a laparotomy was done because of abdominal pain. The whole ileum was involved in the disease process with thickening of the entire wall surrounded by 2 to 4 cm lymph nodes described by the pathologist as 'chronic adenitis'. Three more hospitalizations supervened, during which an ileoscopy to 40 cm showed many ulcerations and severe involvement.

In July 1988, with a white blood count of 17,000/mm³, 86% polymorphonuclear leukocytes and abnormal small bowel x-rays (Figure 1), cyclophosphamide was started at 50 mg daily and increased to 50 mg bid in August. Three weeks later, the patient had a short hospital stay for hypokalemia, recent gastroenteritis and corticosteroid withdrawal symptoms. In April 1989, her white blood count was down to 6700/mm³, 63% polymorphonuclear leukocytes, hemoglobin 12.0 g/dL and erythrocyte sedimentation rate 3 mm/h. Ileoscopy to 35 cm showed a normal mucosa and a normal diameter lumen. The small bowel x-ray (Figure 1) also showed disappearance of ulcers and edema in the terminal ileum; however, discrete residual edema persisted in the jejunum.

One year later, the patient is symptom-free except for amenorrhea, and enjoys a normal life on a maintenance
Cyclophosphamide treatment of Crohn's disease

CASE TWO

A 45-year-old man was treated for Crohn's disease involving the ileum in January 1981. In March, a diagnosis of allergic hepatitis was confirmed and salicylazosulfapyridine was stopped. There were recurrences of the disease in September 1981, July 1982 and February 1983. Each time the patient received corticosteroids for a three month period.

A gastrointestinal series was done in February 1983. Dilated loops and edematous mucosa of the greater part of both the jejunum and ileum were noted. The dilated loops preceded stenotic segments and the terminal ileum had a long 10 cm string sign.

In August 1983, because of diarrhea, rectorrhagia, abdominal pain and a 35 lb (16 kg) weight loss, the patient underwent an ileocolic resection with an ileotransversostomy. Thirty centimetres of both ileum and jejunum were resected; the disease was, however, still present in the jejunum. This resistant disease was treated with 6-mercaptopurine 50 mg bid for six months postoperatively with good results.

In June 1988, the patient complained of diarrhea, a 10 lb (4.5 kg) weight loss, abdominal cramps and steatorrheic stools. He was treated for iron and vitamin B12 deficiencies. In November 1988, he was still complaining of fatigue, a 20 lb (9 kg) weight loss, diarrhea five to six times a day, steatorrhea, a sensation of epigastric blocking and an inability to eat. The laboratory tests showed a white blood count of 18,400/mm³; 76% polymorphonuclear leukocytes and an erythrocyte sedimentation rate of 77 mm/h; total protein was 54 g/L; and vitamin B12 was 135 µg/L.

Small bowel x-ray showed stenosis in segments of the second and fourth parts of the duodenum; the common bile duct filled with barium; the jejunum was totally edematous with the involvement of three short colic segments (Figure 2). During gastroduodenoscopy the proximal portion of the second part of the duodenum was edematous, hyperemic and stenotic near a small punched ulcer. The 6-mercaptopurine which had been started 15 days earlier was stopped because of right upper quadrant pain with dorsal radiation and an inability to eat. This was clearly a very severe, debilitating disease coupled with drug intolerance, so the patient was started on cyclophosphamide 50 mg bid on January 3, 1989. By February 2, 1989 the patient had no complaints except for an occasional mild pain and his usual short loop symptoms. Physical examination was normal except for sensitivity over the terminal ileum; the patient's white blood count was 11,000/mm³.

In June 1989, his white blood count was 6500/mm³, with 77% polymorphonuclear leukocytes and an erythrocyte sedimentation rate of 40 mm/h. Hemoglobin was 11.0 g/dL (normal 14.0 to 18.0); cholesterol 4.6 mM (normal 3.8 to 6.5); triglycerides 1.6 mM (normal 0 to 2.25); iron 14 µM (normal 11 to 30); ferritin 39 ng/mL (normal 29 to 278); α1-glycoproteins 0.80 g/L (normal 0.33 to 0.88); transferrin 2.53 g/L (normal 2.52 to 4.29). Small bowel x-ray showed that the opacification of the common bile duct had disappeared (Figure 2). The cicatricial duodenal stenosis and pre-anastomotic string sign had both persisted, while intestinal edema had lessened.

The patient now enjoys a normal life; he does not have obstructive symptoms arising from the stenotic second part of the duodenum or the terminal ileum.

DISCUSSION

The first patient was quite debilitated by Crohn's disease, unresponsive to doses of prednisone less than 20 mg daily. She had two episodes of pancreatitis, the second being five days earlier than the first in the challenge with 6-mercaptopurine; this phenomenon has also been noted by other authors, and an allergic mechanism has previously been postulated (3-5). This phenomenon appears to implicate both azathioprine and its metabolite, 6-mercaptopurine. In the face of pancreatitis, a drug other than azathioprine or 6-mercaptopurine should be prescribed.

The second patient was also quite debilitated. He continues to have clinical steatorrheic stool, but his general health has improved and he is pain free. Small bowel x-rays now show scarring in the second part of the duodenum and the terminal ileum; the jejunum and ileum have nevertheless improved.

In these two patients, cyclophospha-
mide helped to reduce disease activity. Obviously, a string sign will not be expected to disappear with cyclophosphamide as it would with 6-mercaptopurine. The authors used a dosage of 1 to 2 mg/kg and expect that no more than 150 mg will be necessary. It is important to maintain the white blood cell count above 5000/mm$^3$.

The majority of the cyclophosphamide is converted in the liver into aldophosphamide and two cytotoxic agents: acrolein and phosphoramidemustard. In humans, this drug, with a half-life of 6.5 h, is mostly concentrated in the lymph nodes and in other cells with a rapid turnover. For this reason, cyclophosphamide may be used for the treatment of lymphomas, myelomas and renal graft rejection. In laboratory animals the drug blocks the immunological and inflammatory processes and the hypersensitivity phenomenon.

Cyclophosphamide is an alkylating agent with the ability to substitute an alkyl group for the hydrogen atoms of certain organic compounds (6). The alkylation of DNA is the critical cytotoxic action, breaking the DNA molecule and cross linking its twin strands, thus interfering with DNA replication and RNA transcription.

Research studies have shown that there is an increase of immunoglobulins in inflammatory bowel disease (IBD). Peripheral and mucosal lymphocytes of IBD patients are cytotoxic for colonic epithelial cells. The number of T-lymphocytes is increased in the inflamed mucosa. Destruction of T- and B-lymphocytes by cyclophosphamide seems to suppress cellular and humoral immunity and subsequently the inflammatory process. The authors suggest that this medication may be an alternative to 6-mercaptopurine; its corticosteroid sparing effect enhanced the quality and productivity of life of these two patients.

REFERENCES
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