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Short communication

Aplastic anemia induced by cyclohexylchloroethylnitrousurea

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We report a patient who developed aplastic anemia after three courses of cyclohexylchloroethylnitrousurea (CCNU), procarbazine and oncovine administered after craniotomy and irradiation for brain astrocytoma. To the best of our knowledge, aplastic anemia following CCNU has not been reported previously. The unique course of the disease and implications of this complication are discussed.

Key words: Aplastic anemia, cyclohexylchloroethylnitrousurea.

Introduction

Bone marrow depression is a well-known complication of anti-cancer medications. It usually becomes apparent 7–14 days after treatment.[1] The effect of cyclohexylchloroethylnitrousurea is delayed with a nadir of the white blood cell (WBC) and platelet counts at 3–4 and 4–5 weeks, respectively. Both counts usually normalize within 6–7 weeks.[2]

We report a patient who developed aplastic anemia following three courses of CCNU, procarbazine and oncovine administered after craniotomy and irradiation to the brain for astrocytoma.

Case report

A 35-year-old woman was admitted because of prolonged pancytopenia and fever. Craniotomy had been performed and an astrocytoma was resected 8 months earlier. She had then received irradiation with 600 cGy to the brain followed by three courses of CCNU (160 mg orally on day 1), procarbazine (alternating doses of 50–100 mg orally on days 7–21) and oncovine (2 mg intravenously on days 7 and 28). She had been treated also with carbamazepine, 400 mg twice/day, due to Jacksonian convulsions.

At the end of the third course her hemoglobin level was 9.1 g/dl, the WBC was 2570/mm^3 and the platelet count was 18 000/mm^3 (Table 1). She received a platelet and packed red blood cell (PRBC) transfusion. Fourteen days later she was readmitted because of fever and pancytopenia.

Physical examination results were alopecia, a craniotomy scar and petechiae on the arms and legs. Fever was 39°C, pulse rate was 80/min and regular and the blood pressure was 180/80 mm Hg. The blood counts are shown in Table 1. Serum electrolytes, kidney and liver function tests, urinalysis and chest X-ray were normal.

Blood cultures, obtained from the portocath and peripheral veins, grew *Staphylococcus epidermidis*. On biopsy, the bone marrow as severely hypoplastic. On aspiration, the maturation of the myeloid cells appeared normal with few erythroid progenitors but no megakaryocytes. Carbamazepine was replaced by valporic acid 1000 mg/day and cloxacillin 8 g/day with granulocyte colony stimulating factor (G-SCF) (Leucomx Sandoz/Schering-Plough) 300 mg/day were administered. Four weeks later the WBC count rose to 4000/mm^3 and the G-CSF

Table 1. Blood counts following chemotherapy

	Hemoglobin (g/dl)	WBC (/mm^3)	Platelets (/mm^3)
Prior to chemotherapy	14	5890	346 000
Course 3, day 30	9.1	2570	18 000
Week 6 (Admission)	9.3	1010	19 000
Week 22	10	2000	20 000
Week 26	9.5	1870	44 000
Week 30	12	3830	50 000
Week 34	10.9	3010	60 000

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was discontinued. PRBC transfusions were administered as needed, every 1–2 weeks. However, the patient remained severely thrombocytopenic with spontaneous bleeding from the gums and skin, despite repeated platelet transfusions and administration of transexamic acid (1 g/day). Prednison 60 mg/day was given for 1 month. The spontaneous bleeding stopped. The platelet counts, however, remained very low. Single-donor platelet transfusions were administered whenever the platelet count dropped below 5000/mm^3. Repeated bone marrow aspiration revealed a hypoplastic marrow with normal myeloid and erythropoietic maturation and very few megakaryocytes. Blood counts on weeks 26, 30 and 34 post-chemotherapy revealed only a partial recovery (Table 1). No residual brain tumor was found on serial magnetic resonance imaging.

Discussion

All three cytotoxic agents given to this patient have been previously implicated in bone marrow depression; furthermore, carbamazepine may also cause thrombocytopenia.[3] However, the cessation of this latter medication was not followed by a rise of the platelet count, marrow depression due to oncovine is rare and short lived[2] and the depressive effect of procarbazine is transient in most instances.[2,4] It seems therefore that in our patient the aplastic anemia was most probably caused by CCNU.

Like other nitrosoureas, CCNU selectively depresses the stem cells and, for poorly understood reasons, may produce a late, severe and prolonged bone marrow depression. The nadir of the WBC and platelet counts is usually at 3–4 and 4–5 weeks, respectively. With repeated exposures, the time to recovery becomes progressively longer, up to 10–12 weeks.[2]

A prolonged aplastic bone marrow response following administration of chemotherapy is very rare and to the best of our knowledge has not been reported to date after CCNU. Indeed, only two patients who developed aplastic anemia 3 and 4 years, respectively, following radiation and chemotherapy for malignant epithelial tumors have been reported so far.[5]

It is possible that the aplastic anemia represents a preleukemic phase. Of the patients with aplastic anemia, 1–10% develop a myelodysplastic syndrome or leukemia 4–142 months after the onset of aplastic anemia.[6–8] CCNU may be leukemogenic.[9] The risk of leukemia after treatment of gastrointestinal cancer has increased significantly after the introduction of methyl-CCNU to therapeutic protocols.[10] Increased risk was also reported in patients with brain tumors who were treated with radiation, nitrosourea and, in a few cases, also with procarbazine. Leukemia developed several years after treatment and the risk correlated with the duration of treatment.[11–16] However, severe and prolonged myelosuppression preceded the development of leukemia only in two cases.[15,16]

Our report indicates that CCNU may cause a severe and prolonged bone marrow depression. Long-term follow up is needed to clarify whether this represents a preleukemic phase.

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