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Accidental Overdose of Multiple Chemotherapeutic Agents

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A 35-year-old man with refractory low grade diffuse centroblastic centrocytic non-Hodgkin's lymphoma was treated accidentally with an overdose of multiple chemotherapeutic agents. He was given adriamycin 50 mg/m² and cyclophosphamide 350 mg/m² for 6 days followed by 4 days of vincristine 1 mg/m² and bleomycin 10 mg/m². He was transferred when he developed pancytopenia, fever, severe mucositis, ileus and peripheral neuropathy. He was treated with broad spectrum antibiotics, red cell and single donor platelet transfusions and strict parenteral nutrition. In addition, he was given a continuous infusion of 400 ug daily human recombinant granulocyte macrophage-colony stimulating factor (rh GM-CSF) for 17 days. Intractable severe bleeding from his oral mucositis necessitated treatment with a continuous infusion of 8-ornithine-vasopressin for 8 days. He recovered and could be discharged home after 36 days of hospitalization with normal blood counts and without severe sequelae.

Key Words: *Non-Hodgkins lymphoma, Accidental overdose, rhGM-CSF*

INTRODUCTION

Errors in the administration of chemotherapeutic agents have been reported in the literature. The majority of these reports concern the overdose of a single agent during combination chemotherapy.[1-5] Mistakes are usually decimal point errors or occur by confounding drugs with similar names. Although combination chemotherapy is the treatment of choice for many forms of cancer, accidental overdose of multiple chemotherapeutic agents has not been reported so far. Such an accident forms the basis of this report.

CASE REPORT

This 35-year-old man was diagnosed as having non-Hodgkin's lymphoma in April 1986. He presented with generalized lymphadenopathy, hepatosplenomegaly and peripheral lymphocytosis. A cervical lymph node biopsy was compatible with the diagnosis of a low grade non-Hodgkin's lymphoma which was diffuse centroblastic centrocytic according to the Kiel classification. He was treated with three cycles of the CHOP regimen followed by daily oral leukeran for 6 months. In May 1987, progression of the disease in the abdomen was found. Three cycles of adriamycin, bleomycin and prednisone were given. Trials with daily prednimustine therapy as well as 3 cycles of VP-16 therapy were unsuccessful and the disease was progressing. In November 1988, he was hospitalized for a more aggressive chemotherapy. A MACOP-B-type regimen of adriamycin and cyclophosphamide, alternating with vincristine and bleomycin every other week, combined with daily oral prednisone, ketoconazole and bactrim was scheduled. Due to a misunderstanding, the prescribed chemotherapy was given daily instead of weekly.

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The following doses were administered: adriamycin 50 mg/m² per day and cyclophosphamide 350 mg/m² intravenously for 6 days followed by vincristine 1 mg/m² and bleomycin 10 mg/m² intravenously for 4 days, resulting in a total of 600 mg adriamycin, 4200 mg cyclophosphamide, 80 mg bleomycin and 8 mg vincristine within 10 days.

On the 10th day of chemotherapy, the patient developed fever, generalized weakness and malaise, severe oral and anal discomfort, epistaxis and loss of fresh blood per anus. He was transferred to our hospital.

On admission, the patient was severely ill, hypotensive with a BP of 110/50, PR of 114 and febrile with a temperature of 39.2°C. The oral cavity was hemorrhagic and completely denuded with deep ulcerations and blood clots. The abdomen was painfully distended with markedly diminished bowel sounds. Anal ulcerations were present. Deep tendon reflexes were absent in all four extremities. The spleen was palpable 3 cm below the costal margin. No lymph nodes were palpable.

The following laboratory data were obtained: Hb 8.4 g/l, Hct 25%, WBC 11.980x10⁹/1 with 97% lymphocytes and 0.8% PMN. The platelet count was 8x10⁹/1. Liver and renal function tests were normal, and urin analysis was normal. A chest X-ray was within normal limits. An abdominal X-ray showed distended bowel loops consistent with paralytic ileus. The ECG was unremarkable. The boen marrow aspiration on admission showed an absent normal hemopoiesis but still massive infiltration with B4, B1, HLA-Dr, surface IgG, IgD and lambda light chain positive lymphocytes compatible with the diagnosed lymphoma.

HOSPITAL COURSE

The patient was cared for in a single room with reverse isolation. He was treated with broad spectrum antibiotics, initially with kefzol, tobramycin and azlocillin, which was changed to tienamycin, amikacin and metronidazole because of persistent fever. These antibiotics were maintained until there was recobery of peripheral blood counts. An episode of interstitial pneumonia of unknown origin cleared under the antibiotic therapy. He was allowed no oral intake and was supported with parenteral alimentation. Recombinant human granulocyte macrophage colony stimulating factor (rhGM-CSF) was given 400 ug daily as a continuous infusion for 17 days. No side effects were observed. An episode of intractable severe oral mucosal bleeding leading to hemorrhagic shock was treated with an intravenous infusion of 8-ornithine-vasopressin. He required a total of 21 units of packed red cells and 14 units of single donor platelet concentrates during hospitalization.

A bone marrow examination one week after admission and rhGM-CSF therapy showed three lineage hemopoiesis and only a few remaining small lymphocytes. By this time, the spleen was no longer palpable and the signs of ileus had improved. During the whole hospitalization, the patient showed no evidence of cardiac or hepatic toxicity. Recovery of the first granulocytes was observed after 10 days of rhGM-CSF infusion, corresponding to the 26th day after chemotherapy. He gradually improved. By day 36, his WBC count was 2.2x10⁹/1 with 60% PMN's and his platelet count was 21x10⁹/1. He was discharged home on day 36.

One month later, he was reevaluated at our outpatient clinic. He was well again with a weight gain of 7 kg. Physical examination was normal with the exception of minimal splenomegaly and the absence of the deep tendon reflexes. An echocardiogram showed minimally dilated ventricles with slightly diminished cardiac contractility. The reevaluation of the disease status showed areas of lymphocytic infiltration in the bone marrow aspirates and still significant retroperitoneal, mesenteric and iliac lymphadenopathy on abdominal computed tomography.

DISCUSSION

This patient was treated with 600 mg adriamycin, 4200 mg cyclo-phosphamide, 80 mg bleomycin and 8 mg vincristine within 10 days and suffered mainly from life-threatening pancytopenia, mucositis and ileus. There were no signs of cardiac, hepatic, renal or pulmonary decompensation. Our major concern upon admission was adriamycin toxicity because he had received six time the scheduled dose of adriamycin on 6 subsequent days; this in combination with the other drugs.

The maximum tolerated dose of adriamycin in human beings is not known. In mice, intravenous administration of adriamycin at a dose of 20 to 40 mg/kg is lethal[6] within four days after injection. A single intravenous dose of 10 mg/kg causes a well defined acute cardiac pathology leading to diffuse chronic cardiomyopathy within fifty days.[7] Our patient did not show any signs of acute cardiac decompensation nor signs of arrhythmia. The echocardiographic findings of minimal cardiac dilatation

after discharge may be the effects of this acute overdose as well as those of the previous adriamycin therapy.

No specific antidote was given. Folinic acid has been proposed for vincristine overdose.[8] The effect, however, is controversial.[9] Activated charcoal hemoperfusion has been suggested in reducing blood levels of adriamycin in patients with hepatic disease or accidental overdosage.[10] Since 5 days had already passed since the last dose, we did not perform hemoperfusion.

RhGM-CSF can shorten the period of granulocytopenia following chemotherapy.[11] It is possible, although not certain, that rhGM-CSF has accelerated granulocyte recovery in this patient. It could have been spontaneous recovery 26 days after chemotherapy and 10 days after initiation of rh-GM-CSF infusion.

The tumor response of this refractory lymphoma with a spleen enlarged up to the pelvis prior to therapy was impressive but not complete. It documents the extreme resistance of this type of tumor to chemotherapy. It remains to be seen whether low grade lymphoma can be treated at an earlier stage with high dose chemotherapy or by allogeneic bone marrow transplantation.[12]

In conclusion, this case demonstrates the danger of prescribing anticancer agents by in experienced physicians and underlines the need for specialized institutions for such therapies in order to allow control of dose and concentration and to minimize the possibility of such an accident.

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