Effects of a Single Course of Deferoxamine in Neuroblastoma Patients

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ABSTRACT

A phase II trial of a single 5-day course of deferoxamine in 9 patients with neuroblastomas was completed. Within 2 days of completion of treatment responses were observed in 7 of 9 patients and there was no drug toxicity. These responses were a decrease in bone marrow infiltration and, in one patient, a measurable reduction in her tumor mass. We conclude that deferoxamine given as an 8-h i.v. infusion daily for 5 days at 150 mg/kg/day has antitumor activity.

INTRODUCTION

Deferoxamine (DFO) is produced as an iron chelator by Streptomyces pilosus. After DFO is chemically treated to obtain the metal-free ligand, it is able to bind ferric ion by means of its hydroxamic acid groups. The Fe³⁺-containing complex, ferrioxamine, shows very high chemical stability (K² = 10²¹) (1). Even though DFO can bind other metals, it is mainly the greater affinity for ferric ions that determines its specificity. Previous in vitro studies demonstrated that DFO removes depot iron from hemosiderin and ferritin and, to some extent, transports iron from transferrin; it is not able to withdraw porphyrin iron from hemoglobin, myoglobin, and cytochromes (1).

Blatt and Stitely (2) reported in vitro antitumor activity of DFO against two human neuroblastoma cell lines: this activity was dose dependent and became irreversible only when incubation with DFO (60 μM) lasted more than 48 h. The cytotoxic effect was prevented by coinuculation with greater than stoichiometric amounts of ferric citrate, confirming that iron is required for proliferation of neuroblastoma cells.

These data prompted us to start a phase II pilot study to determine the activity of a single course of DFO in patients with neuroblastomas (3).

MATERIALS AND METHODS

Between November 1988 and June 1989, nine patients, 1.4–15.6 years of age, with histologically proven neuroblastoma were entered in this study (Table 1). All patients had normal liver function, defined as serum bilirubin <1.0 mg/dl and aspartate aminotransferase <30 units/liter, and normal renal function, defined as blood urea nitrogen <20 mg/dl and serum creatinine <1.0 mg/dl. All recovered from hematological toxicity if they were previously treated. The interval between the last dose of chemotherapy and DFO was 6–8 weeks in all pretreated patients.

Prior to treatment all patients had a physical examination and complete blood cell counts, ultrasonography, skeletal survey, and bone scan. Audiometric testing was performed in all patients prior to and 48 h after the last day of DFO treatment. Bone marrow involvement for initial staging and for response was assessed twice, once prior to therapy and on the seventh day, using two needle biopsies and four aspirates from the iliac crests. The presence of tumor cells was evaluated by histological examination and indirect immunofluorescence assay with a panel of monoclonal antibodies (kindly provided by Dr. J. T. Kemhead, Imperial Cancer Research Fund, London, England) (4–6). Quantitation was based on the mean value of three separate visual counts, each of which examined 200 cells.

Six patients were pretreated with combination chemotherapy including high-dose cisplatin (patients 1–6). Three were progressing on this therapy (patients 1–3), and three were in relapse after achieving a "complete" remission (patients 4–6). Three other patients were newly diagnosed (patients 7–9). DFO was administered to three previously untreated patients after bone marrow aspiration and confirmation of diagnosis. Administration was continued during the next 5 days during which time the workup of the patients' extent of disease was being completed. All patients were then given standard cytotoxic therapy.

Disease was staged at the time of diagnosis according to the International Staging System (7). All patients had bone marrow involvement by histological and immunocytological criteria. Four patients had elevated urinary VMA excretion. Six of the 9 patients with evaluable tumors had measurable tumors. Seven patients had increased total and glycosylated serum ferritin levels. Informed consent was obtained from the patients and/or their parents.

The treatment schedule consisted of a single course of DFO at 150 mg/kg/day administered i.v. in normal saline (250 ml/m²) during 8 h for 5 consecutive days.

RESULTS

All nine patients received a single course and all were evaluable for response (Table 2). Patient 7 had complete clearance of bone marrow infiltration according to biopsy and immunofluorescence assay. Seven patients showed a >50% decrease in filtration, and only patient 1 did not change. Three of four patients with increased urinary VMA exhibited a reduction from pretreatment levels, while one patient’s levels remained stable. In patient 4 serial ultrasonography showed a volumetric decrease of 48% in tumor size (from 4.2 x 3.5 x 2.6 to 3.6 x 2.5 x 2.2 cm). In seven patients with increased serum ferritin levels at the time of admission, decrease in total as well as glycosylated ferritin was demonstrated. In all patients, an increase in blood platelet count was also documented after DFO administration.

As far as toxicity is concerned, there were no clinically significant cardiac, pulmonary, renal, or allergic side effects. Preexistent audiometric abnormalities in cisplatin-pretreated patients were not worsened by DFO. No hearing abnormalities were detected in three previously untreated patients.

DISCUSSION

In this study response and acute toxicity were assessed immediately after therapy since our intention was to evaluate a brief course rather than multiple courses. The evaluation of changes in neuroblastoma cells in bone marrow was considered to be the most sensitive indicator of antitumor effect, based...
Upon homogeneous drug distribution and relative stasis of blood flow in the marrow.

These data suggest that DFO given as a 5-day course to patients with neuroblastomas can cause a reduction in tumor growth as well as tumor cytoidal activity. There was a total absence of hematological or visceral toxicity. The "complete" clearance of 2% tumor infiltrates in one patient may be explained by sampling error; however, the inhibition of tumor cell proliferation in seven patients, as well as the measured reduction in tumor volume in one patient, is strong supportive evidence for its anti-neuroblastoma activity.

In conclusion, DFO appears to have antitumor activity in patients with neuroblastomas. The extent and duration of therapy and its application as either single or multiple courses in association with chemotherapy will be the subject of future investigations.

REFERENCES

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