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Case report

Administration of Ethyol (amifostine) to a child with medulloblastoma to ameliorate hematological toxicity of high dose carboplatin

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The first report on the administration of the chemoprotective agent Ethyol (amifostine) in conjunction with high dose carboplatin to a patient in the pediatric/adolescent age group is presented. A 17 year old teenager with recurrent cerebellar medulloblastoma received a total of five courses of high dose carboplatin 2 × 600 mg/m^2 (1200 mg/m^2 total) in each cycle. A complete response has been observed following the third treatment cycle. However, cumulative grade IV hematological toxicity developed following each of the first four treatments. Therefore, the fifth treatment was administered in conjunction with amifostine, at a dose of 2 × 740 mg/m^2. Time to complete hematological recovery (Hb > 100 g/l, granulocytes > 2.0 G/l, platelets > 100 G/l) was 52, 58, 72, 78 and 50 days, respectively, following treatments nos 1, 2, 3, 4 and 5. The duration of grade III–IV neutropenia (< 1.0 G/l) was 3, 7, 8, 10 and 5 days, respectively. The duration of grade II–IV thrombocytopenia (platelets < 75 G/l) was 10, 25, 35, 40 and 32 days, respectively. Grade IV thrombocytopenia (platelets < 25 G/l) lasted for 5, 10, 12, 18 and 3 days, respectively, after each consecutive treatment. The total number of platelet transfusions was 1, 2, 2, 3 and 1, with the transfusion of 6, 9, 11, 11 and 5 units of platelets. The administration of amifostine has not been accompanied by any serious side effect. A short decrease in body temperature and a transient drop of blood pressure have been observed. Although hematological toxicity of high dose carboplatin has not been eliminated by amifostine, we conclude that significant protection was achieved in this situation of progressive bone marrow exhaustion.

Key words: Amifostine, carboplatin, child, medulloblastoma, toxicity.

Introduction

Toxicity of chemo- and radiation therapy is an important issue in pediatric oncology because of acute and long-term effects that increase morbidity and mortality and negatively impact on the quality of life of survivors. The safety concerns that arise from the use of most forms of cancer chemotherapy are well recognized, and are attributable to the relative inability of cytotoxic drugs to effectively discriminate between normal and target tissues. Cumulative toxicity, reflecting the progressive injury to normal tissues after multiple cycles of chemotherapy, represents an important and still unaddressed issue. The consequences of cumulative toxicity are many, including a reduction in the patient's quality of life and limitation in drug tolerance and, importantly, the patient's willingness to accept potential life-sustaining primary and salvage treatment. Therapeutic options as well as the use of supportive care measures such as antibiotics may be severely limited because of prior organ injury, e.g. renal dysfunction after cisplatin therapy or cerebral injury due to bleeding following carboplatin-related thrombocytopenia.

Amifostine (Ethyol), formerly known as WR-2721, represents a new adjunct for the management of cancer patients receiving platinum and alkylating agent-based chemotherapy. The profile that has emerged from preclinical studies is the ability of amifostine to selectively protect a range of tissues including kidney, peripheral nervous system, auditory function and the bone marrow from acute and cumulative toxicity of these forms of chemotherapy. In contrast, neoplastic cells are not protected.[1,2] Moreover, data from several clinical trials suggest enhancement of antitumor efficacy of chemotherapy and radiotherapy by amifostine.[3,4] Additionally, amifostine has been shown to diminish the potential for genotoxic and carcinogenic effects of these same therapeutic modalities, a potential effect of substantial importance for patients who enjoy long-term remissions or possible cure.[5] This ability of amifos-

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tine carries a specific importance for children. Amifostine has not been found to enter the CNS and exhibits a very short systemic half-life,[6,7] which excludes interference with antitumor effects when it is given in conjunction with treatment for brain tumors.

Based on the preclinical data demonstrating the ability of amifostine to reduce hematological toxicity from certain chemotherapy drugs including alkylating agents and platinum analogs[8–15] as well as cisplatin-induced renal[11,15,16] and neurotoxicity,[17] a controlled trial of cyclophosphamide ± amifostine and phase II clinical trials of amifostine and high-dose cisplatin (120–150 mg/m^2) were undertaken in a broad range of tumor types. These data demonstrated that pretreatment with amifostine reduced the depth and duration of cyclophosphamide-induced neutropenia[18] and allowed high doses of cisplatin to be administered safely, which resulted in unexpectedly high tumor response rates.[19,20] Several lines of evidence are available now pointing out the multilineage hemo-protective effects of amifostine, including neutrophils, platelets and red blood cells.[21]

Data from phase I studies[22,23] and randomized phase II trials[24] provide consistent evidence that pretreatment with amifostine reduces the degree and duration of thrombocytopenia following carboplatin administration, allowing a decrease in the need for platelet transfusion and faster hematological recovery.

Carboplatin is one of the most frequently used chemotherapeutic agents for the treatment of solid tumors. The dose-limiting toxicity of carboplatin has been described as hematological toxicity including severe thrombocytopenia.

Here we present the first report on the administration of amifostine to a patient in the pediatric/adolescent age group with the intent to ameliorate cumulative hematological toxicities of carboplatin. Carboplatin has been administered repeatedly to maintain complete remission of a disseminated multifocal medulloblastoma that has completely responded following the third administration of the drug.

Case report

Patient LB, a white male child, presented for the first time at the age of 10 years in June 1987 with the symptoms of headaches, diplopia and gait instability. He was referred to the National Institute of Neurosurgery, where a computed tomography (CT) scan of the brain revealed an infratentorial, midline localized mass originating from the cerebellum and the IVth ventricle. There was no evidence of metastases. After macroscopic complete resection of the cystic tumor, pathological examination showed a medulloblastoma. Postoperative therapy consisted of craniospinal irradiation (49 Gy to the tumor bed and 30 Gy craniospinally). In October 1987 the patient developed tumorous meningitis, therefore he received one dose of 25 mg intrathecal methotrexate in addition to radiotherapy. The patient finished therapy in November 1987 free of tumor and of any symptoms.

In 1988 and 1989 at the same institution intrathecal methotrexate therapy was repeated, single doses of 20 mg methotrexate were administered with prophylactic intent. In June 1989 he developed seizures after intrathecal methotrexate administration and has since then taken anticonvulsive medication.

In October 1992 a routine control CT scan revealed a single suprasellar recurrence of size 6 × 8 mm, which was treated subsequently in November 1992 with stereotactic boost irradiation (11 Gy).

The patient remained stable with no progression of his neurological symptoms until November 1993, when he presented with complaints of frequent hiccups, weight loss and loss of appetite. A magnetic resonance imaging scan of the brain showed multiple intracerebral metastases. One metastatic lesion could be detected in the suprasellar region with a size of 8 mm in diameter, one in the left temporomedial region with a size of 10 mm and a small lesion was suspected on the bottom of the IVth ventricle. He was referred for further treatment to our department in November 1993, 6.5 years after initial diagnosis at the age of 16.5 years. At the time of admission he presented with only minor neurological deficits, such as slight ataxia and slowered psychomotorium, but otherwise showed no physical abnormality.

Because of tumor inoperability and of the history of no previous systemic chemotherapy, we started cytostatic treatment in December 1993. In the period of December 1993–March 1994 he received the following cycles: (1) dibromodulcitol 4 × 1 g/m^2 (on days 1–4), (2) vincristine 2 × 1.5 mg/m^2 (on days 1 and 8), dibromodulcitol 3 × 500 mg/m^2 (on days 1, 8 and 15) and procarbazine 15 × 100 mg/m^2 (on days 1–15), (3)–(5) cisplatin 90 mg/m^2 (day 1), VP-16 3 × 100 mg/m^2 (on days 1–3).

Chemotherapy cycles were administered in 3 weekly–monthly periods, after having reached

complete recovery of neutrophil and platelet counts (absolute neutrophil count; ANC > 1.0 G/l, platelets > 100 G/l). With this therapy a partial response could be achieved with no further neurological progression.

In the next chemotherapy period of March 1994–November 1994 we administered five subsequent cycles of carboplatin (Paraplatin; Bristol, Myers) at a dose of 2 × 600 mg/m^2 in the form of a 1 h infusion on days 1 and 2. A complete tumor response was observed following the third cycle of carboplatin. However, the hematological toxicity of carboplatin became more and more prolonged following the first four treatment courses, requiring frequent platelet transfusions. Therefore, his last, fifth treatment cycle was given with the administration of amifostine. Ethyol was provided on a compassionate need basis by US Bioscience (West Conshohocken, PA). Informed consent was given by the patient and his parent. Amifostine was applied at a dose of 740 mg/m^2 twice per treatment day, both on days 1 and 2. The first dose was administered 15 min prior to the carboplatin infusion i.v. over 15 min, the second dose 2 h following the completion of carboplatin infusion. The patient was kept supine throughout amifostine and carboplatin infusions, with continuous monitoring of his blood pressure and regular body temperature measurements. He received tropisetron (Navoban; Sandoz Pharma, Basel, Switzerland) at a dose of 5 mg as a preventive anti-emetic agent and i.v. fluids as a parallel hydration of 3000 ml/m^2/24 h. In addition to careful monitoring, his hematological parameters, electrolytes, and renal and liver functions were checked before and after amifostine treatment.

The patient completed therapy with the fifth carboplatin cycle in November 1994. A complete remission has been sustained since July 1994. He has remained in very good general condition, stable, with no further changes in his neurological symptoms.

Results

Toxicity of carboplatin

Hematological toxicity, in particular thrombocytopenia, is the major dose-dependent and dose-limiting toxicity of carboplatin. Table 1 summarizes hematological toxicities observed with carboplatin cycles nos 1–5 of 2 × 600 mg/m^2 in patient LB. Toxicities were graded according to SIOP toxicity grading criteria. Grade III–IV, neutropenia and thrombocytopenia could be observed after each of the five carboplatin infusions with a tendency of progressive bone marrow exhaustion after the first four cycles. However, the patient never experienced septic neutropenia or any bleeding episodes throughout this period. Time necessary to total hematological recovery (hemoglobin concentration > 10 g/dl; white blood cell count, WBC > 2.0 G/l; platelet count, PLT > 100 G/l) was 52, 58, 72, 78 and 50 days after carboplatin cycles nos 1–5, respectively. Grade III–IV, neutropenia (< 1.0 G/l) lasted for 3, 7, 8, 10 and 5 days; grade II–IV, thrombocytopenia (< 75 G/l) for 10, 25, 35, 40 and 30 days after subsequent carboplatin cycles, respectively. The duration of unacceptable platelet toxicity (grade IV thrombopenia; PLT < 25 g/l) was 5, 10, 12, 18 and 3 days, respectively. The numbers of platelet transfusions administered were 1, 2, 2, 3 and 1 transfusions; with a total number of 6, 9, 11, 11 and 5 transfused platelet units, after carboplatin cycles nos 1–5, respectively.

Non-hematological toxicities of carboplatin were not found to be significant in this patient.

Table 1. Cumulative hematological toxicity of carboplatin cycles nos 1–5 (cycle no. 5 was given in conjunction with amifostine)

Carboplatin Course No.	No. of days to total recovery HB > 100 G/l WBC > 2.0 G/l PLT > 100 G/l	Duration of grade III–IV neutropenia WBC < 1.0 G/l	Duration of grade II–IV thrombopenia PLT < 75 G/l	Duration of grade IV thrombopenia PLT < 25 G/l	No. of platelet transfusions	Units of platelets transfused
1	52	3	10	5	1	6
2	58	7	25	10	2	9
3	72	8	35	12	2	11
4	78	10	40	18	3	11
5 (with Ethyol)	50	5	32	3	1	5

Toxicity of amifostine

Blood pressure changes during amifostine infusions are shown in Figure 1. A mean drop of 21.5 mmHg (range 12–30 mmHg) in systolic blood pressure was observed at 10–20 min after the start of amifostine infusion. The decrease of systolic blood pressure resolved spontaneously and rapidly within 5–10 min in all four instances without having to interrupt therapy and without requiring treatment with vasopressor agents. A slight decrease in body temperature to 35.9–36.0°C returning to normal levels within 3–4 h was noted after each of the amifostine infusions. Baseline serum calcium and magnesium concentrations decreased further after amifostine infusions but the patient remained asymptomatic; the corresponding values were 2.4 and 2.0 mmol/l for calcium and 0.64 and 0.47 mmol/l for magnesium, measured the day before and 1 day after carboplatin plus amifostine therapy, respectively. Subjective complaints of the patient during amifostine infusion included flushing at the beginning, then nausea, chills, mouth dryness and blurred vision, all resolving spontaneously and without the need for any action to be taken.

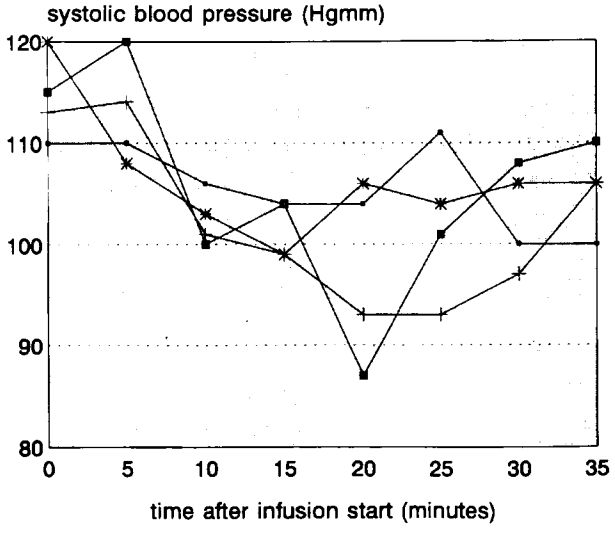

Figure 1. Changes of systolic blood pressure (mmHg) during infusions of amifostine. Amifostine was administered at a dose of 740 mg/m^2 i.v. over 15 min in conjunction with carboplatin infusion no. 5 (2 × 600 mg/m^2) on treatment day 1 [infusion 1 (□) and 2 (+)] and day 2 [infusion 3 (*) and 4 (■)] twice daily, 15 min before the start and 2 h after completion of carboplatin infusion.

Discussion

Carboplatin, an analog of cisplatin, is one of the most attractive new drugs that has been introduced to pediatric oncology recently. The excellent activity of carboplatin has been demonstrated in a number of pediatric tumors. It is active against malignant brain tumors,[25] neuroblastoma,[26] Wilms tumor,[27,28] hepatoblastoma,[29] in germ cell tumors,[30] rhabdomyosarcoma, Ewing's sarcoma, malignant teratomas[31] and even in acute leukemias.[32] Carboplatin has been administered to pediatric patients at different doses and schedules, at a total cumulative dose ranging from 400 to 1875 mg/m^2, divided in 1–5 days infusion schedules.[25–32] Although no randomized studies have been undertaken in children to demonstrate its equivalence or superiority to cisplatin, carboplatin is preferred by many due to the fact that it is less nephrotoxic than the parent compound. However, hematological toxicity of carboplatin is significant and only in part manageable by the administration of cytokines. There remains its toxicity on the platelets, resulting in prolonged thrombocytopenia. The development and degree of myelotoxicity of carboplatin has been correlated to its pharmacokinetics, i.e. to the AUC,[33] and based on this, a dosing formula has been suggested.[33] Recent studies of Riccardi *et al.*[34] have questioned the validity of this formula, finding only a weak correlation between AUC and thrombocytopenia at higher carboplatin dose levels. Thus, at the carboplatin dose level we applied, grade IV thrombopenia occures invariably and is unrelated to the pharmacokinetics of carboplatin.

The dose and schedule of carboplatin for this study have been chosen because of its promising efficacy in brain tumors and also because of pharmacological reasons to achieve a high peak concentration of the drug in the serum and in the CSF. The toxicity of this schedule, according to our previous experience and as shown in this case, is manifested in severe (grade III and grade IV) bone marrow depression, with nadir counts at 7–10 days following the administration of carboplatin and lasting for 7 days to 7 weeks depending on the previous treatment of the patient with this agent. Therefore, any attempt to reduce this toxicity is justified for the reason of delivering highly intensive therapy for a malignant condition. Since myelosuppression is the dose-limiting toxicity of carboplatin, clinical studies of this drug in combination with amifostine are of particular interest.

In the patient we report here, although hematological toxicity of high dose carboplatin has not

been eliminated by amifostine, we conclude that significant protection was achieved, in this situation of progressive bone marrow exhaustion, resulting in faster recovery, a shorter period of grade IV toxicity and less requirements for supportive therapy.

Toxicities of amifostine in this patient were similar to that have been observed in adults, with the exception of blurred vision that has not been described previously. Adverse reactions to amifostine include most importantly a transient reduction in blood pressure in 52% of adult patients treated. Recent data indicate that amifostine-related decrease of systolic blood pressure can be prevented or reduced by the administration of dexamethasone prior to the amifostine infusion(s).[35] Other side effects include nausea and vomiting that is amenable to treatment with standard antiemetics, as was also the case in our patient.

Other effects that have been described during or following amifostine infusion are decrease of body temperature, flushing, feeling of warmth, chills, feeling of coldness, dizziness, somnolence, hiccup and sneezing. These effects never precluded the administration of therapy. A mild decrease of body temperature also occurred in our patient.

A decrease of serum calcium concentration is a known pharmacological effect of amifostine. In the dose range 740–910 mg/m^2, symptomatic hypocalcemia rarely occurs. A decrease of serum calcium was observed in our patient, together with a decrease of serum magnesium concentration. The latter, however, was below normal before the administration of amifostine and could be attributed to prior repeated administration of carboplatin.

In conclusion, amifostine achieved a significant degree of hematological protection from carboplatin-related bone marrow toxicity in our case, with tolerable and transient side effects. A study is planned to investigate systematically amifostine's role in anticancer chemotherapy in children.

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