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Conditioning regimens

Lorazepam for seizure prophylaxis during high-dose busulfan administration

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Summary:

Seizure is a recognized complication of high-dose busulfan (BU) therapy and phenytoin (DPH) is widely used as prophylaxis. A number of adverse effects have been associated with DPH and it may also interfere with BU metabolism. We used lorazepam (median dose 0.022 mg/kg) i.v. or p.o. before each dose and for 24 h after the last dose of BU as seizure prophylaxis to 29 children undergoing hematopoietic stem cell transplantation. The regimen was well tolerated and drowsiness was the only significant side-effect. Twelve patients were able to receive the entire prophylaxis by mouth. No seizure developed during and within 48 h of BU. Concomitant pharmacokinetic studies showed no alternation of the absorption and clearance of BU during lorazepam administration. Lorazepam can be used as an alternative for seizure prophylaxis during high-dose BU treatment.

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High-dose busulfan (BU) is a common component of conditioning regimens for hematopoietic stem cell transplantation (HSCT). It rapidly crosses the blood–brain barrier, with a mean CSF to plasma ratio of 1:1.[1] Neurotoxicity is a well-recognized complication of high-dose BU, with seizures developing in 7.5% of children and 10% of adults if anticonvulsant prophylaxis is not given simultaneously.[2,3] Neurotoxicities include seizures and can occur during BU administration or within 24 h after the last dose, but it rarely happens before the seventh dose.[4–7] It is now common practice to give anticonvulsant prophylaxis along with high-dose BU therapy. Phenytoin (DPH) is an effective and widely used agent for this purpose, but it can be associated with a number of adverse reactions. These include dose-related neurologic and ocular complications, skin rash and exfoliative dermatitis. Cardiovascular changes such as arrhythmias, hypotension and irritation of the veins, have also been reported with parenteral administration. Steady-state DPH concentration is achieved slowly and seizure protection may be inadequate during BU therapy. Phenytoin is known to interact with a number of medications, affecting their serum concentration or therapeutic activities. Alternate agents have been used with the most experience reported with the benzodiazepine class of drugs. Clonazepam, diazepam and clobazam had been used with success.[3,4,8,9] In this report, we review our experience of using lorazepam for seizure prophylaxis in children receiving high-dose BU as part of their HSCT preparative regimen.

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Patients and methods

Patients

From July 1995 to December 2000, 29 children ages 5 months to 19 years were treated with a combination chemotherapy including high-dose busulfan followed by allogeneic ($n = 27$) and autologous ($n = 2$) hematopoietic stem cell transplantation, in the Division of Pediatrics, MD Anderson Cancer Center, Houston, Texas. The patient characteristics are shown in Table 1.

Table 1 Patient characteristics

Number of patients	29
Age, years, median (range)	8 (0.5–19)
Sex	
Male	19
Female	10
Weight, kg, median (range)	21.1 (5–79)
Transplant type	
Autologous	2
Allogeneic	27
Related donor	10
Unrelated donor	17
Diagnosis	
Acute lymphoblastic leukemia	14
Acute myelogenous leukemia	11
Chronic myeloid leukemia	1
Non-Hodgkin's lymphoma	1
Hodgkin's disease	1
Hunter's syndrome	1

Treatment

The details of high-dose busulfan conditioning regimens have been reported previously.[10] Briefly, 25 patients received thiotepa 250 mg/m^2 i.v. on days −9, −8, and −7, BU 40 mg/m^2 p.o. or 0.8 mg/kg i.v. every 6 h for 12 doses, on days −6, −5 and −4, with dose adjustment to maintain an AUC of 1000 to 1500 μM × min and CY 60 mg/kg i.v. on days −3 and −2. Busulfan dose adjustment was required in 17 patients. Four patients received BU 1 mg/kg p.o. every 6 h for 16 doses followed by CY of 120 to 200 mg/kg over 2 to 4 days. Lorazepam was started at 0.02 to 0.05 mg/kg i.v. or p.o. (maximum 2 mg), every 6 h. The lower dose was used for infants under 2 years of age. Lorazepam was given 30 min before each dose of BU and continued every 6 h for four additional doses after the last dose of BU. The dose was reduced by 25 to 50% (rounded to the nearest 0.5 mg) if excessive sedation occurred. Patients were monitored and received supportive care as per institutional protocols or guidelines. Anti-emetic prophylaxis typically included ondansetron and a corticosteroid. Diphenhydramine, promethazine and/or lorazepam were used for breakthrough vomiting. For the prevention of acute graft-versus-host disease, tacrolimus 0.03 mg/kg by continuous i.v. infusion was started on day −2, along with low-dose methotrexate (5 mg/m^2 on days +1, +3 and +6), as described elsewhere.[11]

Results

The actual dose of lorazepam given ranged from 0.015 to 0.045 mg/kg (median 0.022 mg/kg) per dose. No patients developed seizures while receiving or within 48 h of the last dose of BU.

Lorazepam was well tolerated. Twelve patients received all doses of lorazepam by mouth, while the remainder of the patients required some or all of the doses by i.v. administration because of nausea and vomiting. Slight drowsiness was noticed in about half of the patients, but most of these patients were also receiving other anti-emetic medications that were sedating. One patient was noted to have jerky movements of the limbs while asleep. While this phenomenon may be associated with lorazepam, it was not observed when the patient was awake. No dosage adjustment was made. No patient demonstrated disorientation, paradoxical excitement or respiratory depression.

Four patients had adjustment of the lorazepam dosage during therapy. Two patients had the dose increased to alleviate nausea, and both required return to the original dosage because of drowsiness. Two other children had the dose of lorazepam reduced due to excessive sedation or weakness. One patient was switched to DPH due to possible skin allergy to lorazepam.

Discussion

Seizures and other neurologic side-effects are well-recognized complications of high-dose BU therapy. The incidence of neurotoxicity is both age-related and dose-dependent.[3] It was initially suggested that seizures were uncommon in children and prophylactic anticonvulsants were not necessary.[12] However, when BU dosing was calculated on a mg/m^2 basis, thus resulting in larger doses being given, a significantly higher number of children developed neurological complications.[3] Despite DPH prophylaxis, breakthrough seizures were still observed. In one series, three of 14 patients developed seizures despite oral prophylaxis with DPH. This led to the recommendation that all patients should be given a loading dose of DPH, the blood level of DPH should be monitored daily and be in the therapeutic range, and high-dose BU should not begin until this is achieved.[5–7]

The potential deleterious effects of DPH and phenobarbital on the metabolism of BU have been reported. Both of these agents are inducers of CYP 3A4, a major isoenzyme of the CYP 450 system that is responsible for the biotransformation of BU to inactive metabolites.[13] Hassan *et al*[4] showed that co-administration of DPH resulted in a significantly higher clearance, a lower area under the concentration-time curve, and a shorter elimination half-life for the last dose of BU as compared with the first dose. The decrease in steady-state BU levels after 16 doses ranged from 20 to 52%. On the other hand, decreased DPH levels had been found during the administration of antineoplastic agents.[14] This may contribute to the sub-therapeutic DPH levels found in patients who developed seizures despite prophylaxis. Some authors concluded that a standard dose of DPH is insufficient.[6,7]

Because of these limitations, other anticonvulsant prophylaxis has been used during high-dose BU administration. Benzodiazepines are the most common agents employed. Vassel *et al*[3] first reported the use of clonazepam 0.1 mg/kg/day as a continuous i.v. infusion as an anticonvulsant in children receiving a total dose of 600 mg/m^2 of BU. No seizure was observed in 27 patients treated. Shaw *et al*[8] gave clonazepam 0.05 mg/kg twice a day by mouth in a once daily high-dose BU regimen. None of the 20 children developed neurotoxicity. Clonazepam is not available in the parenteral form in the United States, so this is not an option for our patients. Oral diazepam at a dose of 5 mg four times daily has been used with success in adult patients.[4] Schwarer *et al*[9] showed that clobazam, a new benzodiazepine with rapid onset of action, is effective with minimal sedative effect. In addition, Meloni *et al*[15] used a combination of oral phenobarbital and clonazepam to prevent tonic-clonic and myoclonic seizures in a series of 16 patients. No seizure was observed. Benzodiazepine compounds are useful because they have less enzyme-inductive properties and therefore have little or no significant effect on the disposition of high-dose BU.

There is no previous report of using lorazepam as seizure prophylaxis during high-dose BU administration. Lorazepam is an effective anticonvulsant and is indicated in status epilepticus. It is also used as an anxiolytic and a short-acting sedative. At a dose of 0.05 mg/kg (maximum 2 mg) i.v. every 6–8 h, lorazepam is employed for control of chemotherapy-induced nausea and vomiting.[16] It is well tolerated by children. Side-effects of lorazepam include somnolence, dizziness, disorientation and hallucinations have been observed infrequently. Respiratory depression

may occur. Paradoxically, excitement has also been reported in children. Lorazepam is easier to administer than DPH, especially when given parenterally. It also has a longer half-life and causes less respiratory depression than i.v. diazepam.[17] Lorazepam is also effective when given orally, with more than 90% of the drug being absorbed. The onset of action is rapid, beginning 20 to 30 min after ingestion. Another advantage is that monitoring of drug levels is not required.

In the past we have used DPH for seizure prophylaxis and lorazepam as part of the anti-emetic regimen for high-dose BU protocols. In view of the efficacy of other benzodiazepines in preventing seizures and the potential drawbacks of DPH, lorazepam alone was used in this group of our patients. We found lorazepam to be effective in preventing neurotoxicity during high-dose BU therapy. It was well tolerated. Dose adjustment was needed in 15% of our patients. Nearly half of the patients received lorazepam exclusively by mouth. During the study period we also prospectively evaluated the strategy of dose adjustment of oral and intravenous BU based on pharmacokinetic determination. Busulfan concentrations were measured daily and we did not notice any alteration of the absorption and clearance of oral BU by concomitant administration of lorazepam.[10] Similarly, the pharmacokinetic profile of intravenous BU was not affected.

Limitations in this report include the fact that it is a retrospective review of our clinical practice, over a period of more than 5 years. Although the dose of lorazepam was supposed to be that used for anti-emetic purposes, dosage variation occurred. This is due to limited dosage forms available (0.5, 1 and 2 mg tablets; and 2 mg and 4 mg/ml injectables) as well as to the patients' prior tolerance to lorazepam and other sedative agents. These factors affect the dosing precision in our patient population. The lack of neurotoxicity may be related to the lower number of BU doses (12) given to the majority of our patients. However, the amount per dose (40 mg/m^2) was among the highest used in children. In animals it has been shown that BU-associated convulsions resulted from the exposure of the brain to high concentration of this drug or to the accumulation of its metabolites.[18]

In summary, we present the first report of the efficiency of utilizing lorazepam as anticonvulsant prophylaxis in pediatric HSCT patients receiving a BU-based conditioning regimen. Lorazepam given at a dose used commonly for anti-emetic purposes was well tolerated, and its administration did not adversely affect the pharmacokinetic profile of BU.

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