Risk of Seizures in Children Receiving Busulphan-Containing Regimens for Stem Cell Transplantation

Désirée Caselli [1], Anna Rosati [2], Maura Faraci [3], Marta Podda [4], Mimmo Ripaldi [5], Daniela Longoni [6], Simone Cesaro [7], Luca Lo Nigro [8], Olivia Paolicchi [1], Natasha Maximova [9], Maria Cristina Menconi [10], Ottavio Ziino [11], Maria Pia Cicalese [12], Stella Santarone [13], Francesca Nesi [14], Maurizio Aricò [1,15,*], Franco Locatelli [16], Arcangelo Prete [17] on behalf of the Bone Marrow Transplantation Working Group of the Associazione Italiana Ematologia Oncologia Pediatrica

[1] *Pediatric Hematology Oncology and Domiciliary Care, Azienda Ospedaliero-Universitaria A. Meyer Children Hospital, Firenze, Italy*
[2] *Pediatric Hematology Oncology, Neurology, Azienda Ospedaliero-Universitaria A. Meyer Children Hospital, Firenze, Italy*
[3] *Pediatric Hematology Oncology, Hematopoietic Stem Cell Transplant Unit, IRCCS G. Gaslini, Genova, Italy*
[4] *Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy*
[5] *Pediatric Hematology-Oncology, A.O. Pausilipon, Napoli, Italy*
[6] *Pediatric Hematology-Oncology, University of Milano Bicocca, Ospedale San Gerardo, Monza, Italy*
[7] *Pediatric Hematology-Oncology, Policlinico di Verona, Italy*
[8] *Pediatric Hematology-Oncology, Policlinico di Catania, Italy*
[9] *Pediatric Hematology-Oncology, IRCCS Burlo Garofolo, Trieste, Italy*
[10] *Pediatric Hematology-Oncology, Azienda Ospedaliero-Universitaria Pisa, Italy*
[11] *Pediatric Hematology-Oncology, ARNAS Ospedale Civico, Palermo, Italy*
[12] *Pediatric Hematology, Paediatric Immunology and Bone Marrow Transplantation Unit, San Raffaele Scientific Institute and San Raffaele Telethon Institute for Gene Therapy (HSR-TIGET), San Raffaele Scientific Institute, Milan, Italy*
[13] *Pediatric Hematology-Oncology, Pescara, Italy*
[14] *Pediatric Hematology-Oncology, Ospedale Sant'Anna, Turin, Italy*
[15] *Pediatric Oncology Regional Network, Istituto Toscano Tumori (I.T.T.), Firenze, Italy*
[16] *Pediatric Hematology-Oncology, IRCCS Bambino Gesù Children Hospital, Rome, Italy*
[17] *Pediatric Hematology-Oncology, University of Bologna, Bologna, Italy*

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Busulphan (BU) is associated with neurotoxicity and risk of seizures. Hence, seizure prophylaxis is routinely utilized during BU administration for stem cell transplantation (SCT). We collected data on the incidence of seizures among children undergoing SCT in Italy. Fourteen pediatric transplantation centers agreed to report unselected data on children receiving BU as part of the conditioning regimen for SCT between 2005 and 2012. Data on 954 pediatric transplantation procedures were collected; of them, 66% of the patients received BU orally, and the remaining 34%, i.v. All the patients received prophylaxis of seizures, according to local protocols, consisting of different schedules and drugs. A total of 13 patients (1.3%) developed seizures; of them, 3 had a history of epilepsy (or other seizure-related pre-existing condition); 3 had documented brain lesions potentially causing seizures per se; 1 had febrile seizures, 1 severe hypo-osmolality. In the remaining 5 patients, seizures were considered not explained and, thus, potentially related to BU administration. The incidence of seizures in children receiving BU-containing regimen was very low (1.3%); furthermore, most of them had at least 1—either pre-existing or concurrent—associated risk factor for seizures.

INTRODUCTION

Busulphan (BU) is an alkylating agent, employed for over 30 years in a variety of conditioning regimens for stem cell transplantation (SCT) as an alternative to total body irradiation (TBI). Initially introduced as a palliative treatment for chronic myeloid leukemia in adults [1], it was then used as a myeloablative drug in association with cyclophosphamide [2]. BU was rapidly recognized as an effective conditioning regimen for a variety of malignant and nonmalignant hematologic diseases, providing a good alternative to TBI when it was administered at myeloablative dose (16 mg/kg) [3].

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* Correspondence and reprint requests: Maurizio Aricò, Coordinatore Rete Regionale Oncoematologia Pediatrica, Istituto Toscano Tumori, Viale Pieraccini 6, 50139 Firenze, Italy.
E-mail address: maurizio.arico@ittumori.it (M. Aricò).
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Recently, it has been used, in combination with melphalan and fludarabine, in the so-called reduced-intensity conditioning regimens in adults and children at a dosage of 3.2 or 6.4 mg/kg [4].

A limited degree of plasma protein binding allows BU, unlike other lipophilic alkylating agents such as melphalan, to easily cross the blood-brain barrier, thus achieving levels in cerebrospinal fluid that are similar to those in plasma [5,6]. Neurotoxicity was associated with BU in animals [7] and in humans, also favored by an altered blood-brain barrier [8]. The incidence of neurotoxicity after BU-based conditioning therapy is reported up to 10% in adults [9], and approximately 7% in children [10]. Vassal et al. reported that higher doses (600 mg/m^2 or 16 mg/kg) were associated with an increased probability of neurotoxic manifestations [5]. Generalized seizures are the main manifestation of BU neurotoxicity. They are more frequent in older patients and appear to be dose dependent, both in children and adults [6,10,11]. In adults, seizures typically occur in the third or fourth day of BU administration, probably as a result of drug accumulation [6,8,12]. Even without overt seizure activity, electroencephalogram abnormalities can occur in up to 60% of patients [11,13,14].

Various antiepileptic drugs (AEDs) have been used for seizure prophylaxis, including phenobarbital sodium, benzodiazepines (clonazepam, lorazepam), and phenytoin [15-19].

It is worth mentioning that between .5% and 1% of children in the general population experience a nonrecurrent, single, unprovoked convulsive episode [20]. Considering both the potential pharmacokinetic drug interactions between AEDs and BU [21] and the effective risk of BU-related seizures, we decided to re-evaluate the current standard practice of using of AEDs for seizure prophylaxis in patients receiving BU before hematopoietic SCT [22]. With the aim to evaluate the incidence of seizures in children treated with BU, we performed a retrospective analysis among the pediatric hematology-oncology centers of the Associazione Italiana Ematologia Oncologia Pediatrica.

MATERIALS AND METHODS

All of the Associazione Italiana Ematologia Oncologia Pediatrica (www.aieop.org) centers were invited to participate in a retrospective data collection on all children receiving BU as part of their conditioning regimen for SCT between 2005 and 2012.

Data on route of administration, drug monitoring, seizure-specific risks factors, neurological associated conditions, seizure prophylaxis, and occurrence of seizures were collected on a specific form and pooled.

Only seizures occurring during or soon after (up to 2 days) last BU administration were considered to be potentially related [15].

RESULTS

A total of 954 transplantations performed in pediatric patients were reported by the 14 participating centers. In 637 (66%) of them, BU was administered orally, whereas in the remaining cases BU was given i.v.. All patients received prophylaxis of seizures according to the local policies (Table 1).

Seizures were reported in a total of 13 patients (1.8%), 8 males and 5 females, with a median age of 9 years. The source for stem cells was autologous in 5 patients and allogeneic in 8. BU had been administered orally in 7 children and i.v. in 6.

Of the 13 reported episodes, only 5 occurred within the time interval during which BU is expected to be present in the peripheral blood, ie, on days -6 (n = 2), −5, −3, −1. The remaining episodes of seizures were observed between day +1 and day +86 from transplantation (Table 2).

Of the 13 patients who developed seizures, 3 had a history of epilepsy (or other seizure-related pre-existing condition); 1 had febrile seizures; 3 had a brain lesion documented by MRI, considered by the attending physicians as a possible cause for seizures; 1 developed seizures during documented severe plasma hypo-osmolality, in the presence of carbamazepine plasma levels exceeding the therapeutic range (22 mg/L; upper normal limit 10 mg/L). Thus, only in the remaining 5 patients the seizures were considered fully unexplained by any concurrent factor, and thus most likely related to BU administration (Table 2).

Table 1
List of Drugs Used, in Decreasing Order, for Prophylaxis of Seizures in Children Receiving Busulphan-containing Regimens for Stem Cell Transplantation

Drug (Route of Administration)	Schedule
Carbamazepine (orally)	10-15 mg/kg/d
Clonazepam (orally)	.1-.2/mg/kg/d
Valproate (orally)	10-20 mg/kg/d
Phenobarbital (orally)	3 mg/kg/d
Dintoine (orally)	5-10 mg/kg/d
Lorazepam (intravenously)	.03-.06 mg/kg/d
Lorazepam (orally)	.02-.05 (max. 2 mg) every 6 h, 30 min. before BU administration
Levetiracetam (orally)	20 mg/kg/d
Midazolam (intravenously)	.05 mg/kg/d

DISCUSSION

Acute symptomatic seizures are seizures occurring at the time of a systemic damage or in close temporal association with a documented brain damage [23]. The risk of experiencing an acute symptomatic seizure is 3.6% in an 80-year lifespan [24]. The frequency of BU-related seizures is reported in the literature in the range of 10% in the absence of specific prophylaxis [5,8,15]. This supported the development of anticonvulsant prophylaxis as a standard of care also in pediatrics [25]. Yet, this recommendation remains based on a few old studies, mainly retrospective, with very limited number of patients. Subsequent modifications in the transplantation regimens, supportive care, and monitoring strategies are, thus, not taken into account.

In the present study of a large pediatric cohort of 954 transplantations, in which all patients received a prophylaxis, (almost invariably orally, with carbamazepine accounting for over one third of the cases, and clonazepam, valproate, phenobarbital and dintoine in about 100 cases) the frequency of seizures was 1.3%. This finding of such a low incidence of seizures might be considered to lend some support to the continuous use of the prophylaxis. Yet, many concerns have been raised about the real utility of prophylaxis [26,27]. Some authors define this persistent recommendation as “an example of an outdated clinical practice that persist despite a paucity of good quality supporting medical evidence [22].” Furthermore, the use of different regimens of prophylaxis, with different drugs and different mechanisms of action [15] as observed also in our study, without any drug monitoring confirming the achievement of effective drug levels, or even by using drugs which are expected to become therapeutic in a longer time interval, might simply represent an additional variable in the peritransplant phase. Furthermore, in the absence of any prophylaxis, a comparably low incidence (1.8%) of seizures was observed in an old report of a small series of 57 children [10], whereas no seizures at all were observed in a large series of 344 adults, leading the authors to challenge the need for prophylaxis [22]. The current study of a large series of children shows a frequency of seizures comparable to that observed in untreated adults and children.

Table 2
Main Features of Thirteen Children Who Developed Seizures during SCT during or after a Busulphan-containing Preparative egimen

Case No.	Gender/ Age, yr	Stem Cells Source	BU Route	Day of Onset and Seizure Type	EEG	Prophylaxis and Notes
Likely Busulphan-Related						
1	F/1.3	UCB	Oral	−6; repeated episodes of ocular deviation	Irritative	Lorazepam i.v. since 24 h before BU; previous seizures; brain CT scan: left hypoplasia, scattered calcifications; possible ischemic origin.
2	M/13	ALLO	Oral	−6; generalized	Normal	Carbamazepine since 5 days before BU; hyponatremia (122 mEq/L); on therapy with carbamazepine, plasma levels exceeding therapeutic range (22 mg/L; range, 4 to 10).
3	M/16	Autologous	Oral	−5; generalized	Normal (on day -2)	Partial complex epilepsy, arachnoid cyst, on antiepileptic therapy
4	M/19	Autologous	Oral	−3; myoclonus	Bilateral spikes	Lorazepam i.v. since 24 h before BU
5	M/5.7	Autologous	Oral	−1; partial seizure evolving to generalized seizure	Irritative	Carbamazepine since 24 h before BU. Normal MRI
Case	Gender/ Age, yr	Stem Cells Source	BU Route	Seizure Type	EEG	Notes
Unlikely to be Busulphan-Related						
6	M/5	Autologous	i.v.	+1; generalized		Phenobarbital since 24 h before BU.
7	M/16	ALLO	i.v.	+1; generalized	Irritative	Epilepsy, on therapy with levetiracetam; clinical picture suggestive for PRES
8	F/13	MRD	i.v.	+1; generalized	NP	Dintoine since 24 h before BU. MRI: aspecific lesions
9	M/6	AUTO	Oral	+10; generalized		Dintoine since 24 h before BU.
10	F/9	MRD	i.v.	+13; generalized	Irritative	Dintoine since 24 h before BU. Previous encephalopathy; normal CT
11	F/6	PMRD	i.v.	+15; generalized	Irritative	Dintoine since 24 h before BU
12	F/9	MRD	i.v.	+2, +37; generalized	Irritative; frontal foci	Dintoine since 24 h before BU; MRI cortical-subcortical alterations, hyperintense on FLAIR
13	M/11	MRD	oral	+86; generalized		Dintoine since 24 h before BU. MRI: frontal nodal lesion (1 cm.), perilesional edema;

EEG, electroencephalogram; ALLO, allogeneic; UCB, umbilical cord blood; MRD; matched related donor; PMRD, partially matched related donor; CT, computed tomography; MRI, magnetic resonance imaging; PRES, Posterior Reversible Encephalopathy Syndrome; FLAIR, fluid attenuated inversion recovery.

Despite the prophylaxis, 13 patients in our study were reported to have developed seizures, which, at first evaluation, could have been considered as BU related. Yet, at a careful revision, the majority of them showed concurrent or associated factors, which could, per se, make those children at risk for seizures. In particular, 2 of them had a history of epilepsy and were on antiepileptic therapy (not prophylaxis), 1 had previous seizures with evident brain abnormalities at computed tomography scan, and another had febrile seizures; a fifth child developed seizures during inappropriate antidiuretic hormone secretion, documented by concurrent severe hyponatremia, associated with, or possibly related to, the concurrent high plasma levels of carbamazepine; these event may be considered to be potentially related [28]. Three additional patients had either a history of undefined encephalopathy or gross abnormalities at magnetic resonance imaging, which in 1 case had justified antiepileptic therapy with phenobarbital. Thus, of the total 13, only in 5 patients the seizures were finally considered as really unexpected. They are either males or females, ages between 5 and 19 years, undergoing autologous ($n = 3$) or allogeneic ($n = 2$) transplantations. Based on this finding, the proportion of patients who developed BU-related, otherwise unexplained seizures might be as low as .75%.

Another open issue, ie, potential interference with BU pharmacokinetic [21], could also be worth investigation, but this fell outside the scopes of this retrospective survey.

In conclusion, in the present large series of children, the proportion of children exposed to BU-containing regimen for SCT while receiving specific prophylaxis who develop BU-related seizures appears to be very low, in the range of less than 1%. Furthermore, anticonvulsants, as most drugs, may have side effects and can alter the pharmacokinetic of other drugs used during SCT [29,30]. Yet, whether children can be given BU without prophylaxis is a question, which cannot be answered with the present data. A prospective study on this issue appears warranted.

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Live Attenuated Varicella-Zoster Vaccine in Hematopoietic Stem Cell Transplantation Recipients

Nicolas C. Issa [1,2,3,*], Francisco M. Marty [1,2,3], Houry Leblebjian [4], Alicia Galar [1,3], Margaret M. Shea [1], Joseph H. Antin [2,3], Robert J. Soiffer [2,3], Lindsey R. Baden [1,2,3]

[1] *Division of Infectious Diseases, Brigham and Women's Hospital, Boston, Massachusetts*
[2] *Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts*
[3] *Harvard Medical School, Boston, Massachusetts*
[4] *Department of Pharmacy, Dana-Farber Cancer Institute, Boston, Massachusetts*

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Hematopoietic stem cell transplantation (HSCT) recipients are at risk for varicella-zoster virus (VZV) reactivation. Vaccination may help restore VZV immunity; however, the available live attenuated VZV vaccine (Zostavax) is contraindicated in immunocompromised hosts. We report our experience with using a single dose of VZV vaccine in 110 adult autologous and allogeneic HSCT recipients who were about 2 years after transplantation, free of graft-versus-host disease, and not receiving immunosuppression. One hundred eight vaccine recipients (98.2%) had no clinically apparent adverse events with a median follow-up period of 9.5 months (interquartile range, 6 to 16; range, 2 to 28). Two vaccine recipients (1.8%) developed a skin rash (one zoster-like rash with associated pain, one varicella-like) within 42 days post-vaccination that resolved with antiviral therapy. We could not confirm if these rashes were due to vaccine (Oka) or wild-type VZV. No other possible cases of VZV reactivation have occurred with about 1178 months of follow-up. Live attenuated zoster vaccine appears generally safe in this population when vaccinated as noted; the overall vaccination risk needs to be weighed against the risk of wild-type VZV disease in this high-risk population.

INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) recipients are at increased risk for varicella-zoster virus (VZV) reactivation. VZV disease after HSCT varies depending on type of transplantation (autologous versus allogeneic) but is reported to be as high as 30% to 53%; the highest risk has been reported to occur during the first year after transplantation and may be associated with visceral dissemination [1-8]. Antiviral prophylaxis has been shown to prevent VZV reactivation;

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* Correspondence and reprint requests: Nicolas C. Issa, MD, Division of Infectious Diseases, Brigham and Women's Hospital, 75 Francis St, PBB-A4, Boston, MA 02115.
E-mail address: nissa@partners.org (N.C. Issa).
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