TECHNICAL REPORT

Intravenous Busulfan, Dimethylacetamide and neurotoxicity after high-dose pretransplant conditioning chemotherapy

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INTRODUCTION

Pursuing more efficacious and less toxic allogeneic stem-cell transplant (allo-SCT) conditioning therapy, intravenous (IV) Busulfan, Busulfex™, (Bu) was introduced in 1999 [1]. Its combinations with Cyclophosphamide (Cy) or with the nucleoside analog Fludarabine (Flu), have led for more than a decade high-dose chemotherapy for allo-SCT for patients with acute and chronic myeloid leukemia (AML, CML) and myelodysplastic syndrome (MDS) [2–4]. It is increasingly being advocated in high dose chemotherapy (HDC) with autologous SCT for relapsed Hodgkin and non-Hodgkin lymphomas and myeloma [5–8], where it may confer an advantage over previous standard of care with BCNU, etoposide, cytarabine and melphalan (BEAM) and high-dose Melphalan, respectively [6, 7]. Regarding allo-SCT for AML and MDS, Bu-based conditioning results in better overall survival than Cy-total body irradiation (TBI) [9, 10], and yields lower risk for severe graft versus host disease [11]. While IV Bu represents an improvement over TBI, there remain concerns with the formulation, initially expressed by the FDA expert reviewer in 1999 [1]. These concerns were not related to busulfan itself, but rather to its solvent vehicle including N,N-dimethylacetamide (DMA) [12, 13]. In contrast, the sponsor, Orphan Medical Inc. (OMI) (Minnetonka, MN), claimed a DMA-based solvent to be safe, based on a published trial using DMA as an anti-cancer agent [14]. However, in his review of the phase II data underlying the approval of Busulfex, the FDA expert examiner surmised that the total amount of DMA given in HDC may be enough to cause significant toxicities [1]. Occupational DMA exposure was associated with both neurological and hepatic toxicity, and in experimental systems it also caused reproductive toxicity [14–16].

In reference to possible DMA toxicity, the phase II study report submitted by OMI listed a high incidence of neurological toxicities: 84% insomnia, 72% anxiety, 30% dizziness and 23% depression following IV Bu infusion. Fewer patients suffered more serious problems, including delirium (2%), agitation (2%), confusion (11%), hallucinations (5%) and encephalopathy (2%) [1]. In our use of IV Bu-based conditioning, we recorded six patients who developed hallucinations, agitation, delirium, and in two cases deep stupor. These neurologically deranged states lasted for almost 2 months in one patient before he recovered, while in one patient it deteriorated into an encephalopathy with progressive, irreversible coma before he expired 5 weeks post-SCT. Two patients recovered within 10 days from the onset of the problems; in two patients altered mental status started days after recovery from treated bacteremia (Table 1).

DISCUSSION

The current Bu-formulation with DMA-PEG is safer and better tolerated than oral Bu in HDC [9–11], but there are lingering concerns that may be related to DMA [1, 13]. Unfortunately, it is impossible to evaluate IV Bu with and without DMA, because the only currently approved IV Bu formulation contains DMA. We made the following observations when we changed from oral to IV Bu in HDC: First, there appears not only to be a reduction in venoocclusive disease/sinusoidal obstruction syndrome (VOD/SOS) of the liver, but also a change in its clinical picture. Classical VOD/SOS has a rapid onset after SCT, typically within the first 3–4 weeks, followed by a gradual decline of the patient's condition, leading to hepato-renal/multiorgan failure and death within a few weeks [17–19], whereas milder cases had a subacute onset followed by gradual recovery. This has commonly been replaced by an episode of "silent" transaminitis and hyperbilirubinemia occurring within 10–14 days after IV Bu in 30–40% of the patients, which typically resolves within 7–10 days. Fewer cases of serious treatment-related VOD/SOS manifest themselves either early (as in classical VOD) or later, with some patients developing liver failure as late as 8–12 weeks after SCT with subsequent decline and death [4, 20–24]. We hypothesize that this delayed presentation of serious, life-threatening VOD/SOS may be due to an interaction between DMA and Bu in the generation of liver toxicity, as oral Bu-(Cy) associated VOD historically manifested itself early, within the first few weeks after exposure. Delayed onset of serious liver toxicity, 8–12 weeks after exposure, is reminiscent of that described by Choi after occupational DMA exposure [15].

Second, there is concern about potentially serious neurological toxicity with the DMA-PEG formulation. In the pivotal phase II studies, OMI reported that the maximum DMA dose given as part of IV Bu, Busulfex™, was about 42% of the maximum tolerated dose on a mg/kg body weight basis, extrapolated from the phase I study of DMA as an anti-cancer agent [10]. The description of the IV-Bu serious advers event (SAE) profile is strikingly similar to that experienced by all ten patients who received DMA at a total dose of 400 mg/kg/day for at least 3 days in its phase I study [14]. Three of the ten patients at the highest dose level developed hypotension and a shock-like syndrome that cleared in two of

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Table 1. Clinical characteristics and risk factors that may promote neurotoxicity.

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age > 50	Yes	Yes	Yes	Yes	Yes	Yes
Hx of brain radiation or TBI	Whole-brain radiation	TBI-conditioning with prior SCT	No	No	No	No
Underlying disease	t-AML	Relapsed AML for 2nd SCT	P53-mutated ALL	High-risk Myeloma	High-risk Myeloma	High-risk Myeloma
Conditioning Chemotherapy	fludarabine, 40 mg/m^2 IV and Bu at 130 mg/m^2 IV, daily (Flu-Bu) (days −6 to −3)	fludarabine, 40 mg/m^2 IV and Bu at 130 mg/m^2 IV, daily (Flu-Bu) (days −6 to −3)	Clofarabine 40 mg/m^2 IV and Busulfan 100 mg/m^2 IV, daily (Clo-Bu) (days −6 to −3)	Bu on days −7, to −4 daily AUC of 4000 μMol-min/day and melphalan 70 mg/m^2 per day on days −2, −1	Bu on days −7, to −4 daily AUC of 4000 μMol-min/day and melphalan 70 mg/m^2 per day on days −2, −1	Bu on days −7, to −4 daily AUC of 4000 μMol-min/day and melphalan 70 mg/m^2 per day on days −2, −1
Peripherally Neurotoxic chemo before SCT	CDDP	No	Vincristine	No	No	No
Centrally Neurotoxic chemo before SCT	Ifosfamide, Ara-C	Ara-C	No	No	No	No
Immunotoxins (Inotuzumab etc)	No	No	Inotuzumab, Blinatumomab	No	No	No
Organic brain conditions[b]	Carotid atherosclerosis s/p endarterectomy	SDH[a] requiring surgical intervention	No	No	No	MRI reflective chronic small vessel ischemic change
Spinal cord conditions[c]	No	Herniated disk s/p removal of Schwannoma of spinal cord	No	No	No	Numerous vertebral compressions, requiring Vertebroplasty
Hx of confusion/ delirium with other chemo	Triapine, Ara-C	No	Inotuzumab, Blinatumomab	Only in the setting of hypercalcemia	No	Dizziness in the setting of hypercalcemia
Hx of head trauma	Fell, suffered head laceration	No	No	No	No	No
Others	Neuropathy after chemo, Brain atrophy	Neuropathy after previous chemo	No	No	No	No

[a]SDH - subdural hematoma.
[b]Brain Mets.
[c]Tumors, spinal surgeries or radiation.

them, although the third patient subsequently developed "meningismus" with a negative work-up for infection and expired [14]. Because of the known association of DMA with serious toxicities in animals and humans it is considered a class II agent, i.e., its use in pharmaceutical formulations should be very limited, or preferably avoided [13, 25, 26]. In fact, the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use, Step 4, currently limits the daily exposure of DMA to 10.9 mg [26]. This recommended maximal exposure is exceeded by at least 1000–1500-fold when adults receive a myeloablative 4-day course of IV Bu/DMA with Cy or Flu [13, 22–24].

We herein report six patients who experienced hallucinations, agitation, delirium, and deep stupor in one patient lasting for almost 2 months before clearing. One additional patient developed stupor, which advanced into encephalopathy, irreversible coma and death. Those cases illustrate that it may be advisable to heed the FDA expert reviewer's concern and exercise caution with the DMA-containing Bu formulation, Busulfex™, at least in patients with preexisting CNS history of radiotherapy or cerebrovascular disease.

Further, OMI claimed that the maximum DMA dose delivered with their BuCy2 regimen was about 42% of that reported toxic by Weiss [14]; however, a more careful calculation shows that the dose given over 4 days exceeds 60%. In addition, many centers have moved from dosing based on body size and utilize pharmacokinetic (PK) dose guidance for IV Bu [21, 23, 24]. Due to interindividual heterogeneity in human drug metabolism, patients who rapidly metabolize busulfan may now receive IV Bu doses ≥200 mg/m^2. This translates into a DMA dose >80% of the dose reported by Weiss as toxic [14]. Therefore, we suggest that there may not only be a risk for DMA-associated toxicity, but also a potential for serious clinical interactions between DMA and Bu, and with other components of multiagent regimens, which may be further obfuscated by interindividual differences in drug metabolism.

CONCLUSION

We suggest that caution should be exercised with use of IV Bu in patients who have an underlying organic brain disorder, or who have received brain XRT or immunoconjugates with a potential for causing CNS adverse events.

DATA AVAILABILITY

Raw data were generated at the University of Texas MD Anderson Cancer Center. Derived data supporting the findings of this study are available from the corresponding author JLR upon reasonable request.

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AUTHOR CONTRIBUTIONS

JLR contributed to writing in each section of the paper. GSP contributed in summarizing the reports and table. KHC contributed in verifying and summarizing the reports. YN, BV, and BSA have made a substantial contribution to the concept and design of the paper.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL

Informed consent was obtained from patient and family prior to publishing the cases.

ADDITIONAL INFORMATION

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