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Autologous

A Comprehensive Assessment of Toxicities in Patients with Central Nervous System Lymphoma Undergoing Autologous Stem Cell Transplantation Using Thiotepa, Busulfan, and Cyclophosphamide Conditioning

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A B S T R A C T

High-dose therapy and autologous stem cell transplantation (ASCT) with thiotepa, busulfan, and cyclophosphamide (TBC) conditioning has emerged as an effective postinduction treatment strategy for patients with primary central nervous system lymphoma (PCNSL) or secondary central nervous system lymphoma (SCNSL), but it is associated with considerable toxicity and transplantation-related mortality (TRM) in the modern era. Forty-three adult patients with chemosensitive PCNSL or SCNSL underwent TBC-conditioned ASCT between 2006 and 2015. Twenty-eight of these patients received pharmacokinetically (PK)-targeted busulfan dosing. The median number of clinically relevant individual grade ≥3 nonhematologic toxicities per patient was 5. We found no association between pretransplantation patient characteristics and the presence of more than 5 grade ≥3 nonhematologic toxicities. Patients with elevated first-dose busulfan area under the curve values did not experience more toxicity. Paradoxically, patients treated with more than 2 regimens before undergoing ASCT had lower first-dose busulfan AUC values. With a median follow-up among survivors of 20 months, 1-year progression-free survival (PFS) and overall survival (OS) from the time of ASCT were 83% and 87%, respectively. Although this study reaffirms the favorable PFS and OS associated with TBC-conditioned ASCT for PCNSL or SCNSL, this treatment strategy carries a large toxicity burden.

INTRODUCTION

Durable disease control in central nervous system lymphoma (CNSL) is elusive even for patients who attain complete remission (CR) with induction therapy, thereby making consolidation therapy critical to overall survival (OS) [1,2]. High-dose chemotherapy (HDT) followed by autologous stem cell transplantation (ASCT) has proven to be an effective consolidative approach in eligible patients. We have previously shown that HDT-ASCT performed in first remission for CNSL affords the omission of potentially neurotoxic whole brain radiotherapy (WBRT) [3,4]. Patients with recurrent or refractory CNSL conditioned with thiotepa, busulfan, and cyclophosphamide (TBC) before ASCT have shown favorable progression-free survival (PFS) and OS [3,5,6].

Our retrospective analysis of 17 patients with recurrent primary CNSL (PCSNL) or secondary CNSL (SCNSL) who had achieved CR after salvage methotrexate (MTX)-based induction regimens proceeding to TBC-conditioned ASCT found a 3-year PFS and OS of 93% [3]. That study found relatively few grade ≥3 toxicities, no grade 4 toxicities, and no treatment-related deaths. In a phase II study conducted at our center, 26 patients with newly diagnosed PCNSL in chemosensitive remission after rituximab, methotrexate, procarbazine, and vincristine induction proceeded to first remission consolidative

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HDT-ASCT with TBC conditioning [7]. The 2-year PFS and OS for the patients who underwent transplantation were 75% and 81%, respectively, superior to the survival rates reported in a previous trial of HD-MTX/cytarabine followed by carmustine, etoposide, cytarabine, and melphalan (BEAM)-conditioned ASCT [8]. Although the regimen was clearly efficacious, 3 of the patients who underwent transplantation with TBC conditioning (11.5%) died secondary to transplantation-related mortality (TRM), a higher rate than expected for HDT-ASCT in patients with other non-Hodgkin lymphomas (NHLs), indicating a toxic regimen in a potentially more susceptible population [7,9]. The 3 deaths were attributed to infection, skin toxicity (Stevens-Johnson syndrome), and severe colitis (possibly autologous graft-versus-host disease [GVHD]).

Predictable and precise dosing of busulfan, an alkylating agent commonly used in hematopoietic cell transplantation conditioning, has proven to be imperative in ameliorating toxicity while ensuring effective myeloablation. Individualized, targeted pharmacokinetically (PK)-directed dosing of i.v. busulfan (both at 6-hour intervals and daily) has become more routine, yielding a more predictable area under the curve (AUC) within a desired therapeutic range [10-12]. In 2012, our Adult Bone Marrow Transplantation Service at Memorial Sloan Kettering Cancer Center (MSKCC) began using daily busulfan PK levels to achieve a target AUC range with the TBC conditioning program to maintain myeloablation while reducing toxicity. Our aforementioned phase II study in which TRM was observed in 11.5% of patients did not incorporate busulfan PK dose targeting [7].

In the present study, we sought to analyze potential factors contributing to the TRM associated with consolidative TBC conditioning before ASCT. To that end, our primary aim was to evaluate and catalog all of the characteristic high-grade toxicities of TBC conditioning for ASCT in patients with CNSL at our institution. We hypothesized that certain baseline pretransplantation patient characteristics would predict for incurring more grade 3-5 nonhematologic toxicities. We also aimed to evaluate the association of busulfan AUC values with pretransplantation patient characteristics and the development of treatment-related toxicities. We hypothesized that higher-than-expected busulfan AUC values would correlate with more observed toxicity.

MATERIALS AND METHODS

Forty-three eligible patients age ≥18 years with newly diagnosed or relapsed chemosensitive PCNSL or SCNSL proceeding to consolidative TBC-conditioned HDT-ASCT between December 2006 and October 2015 were included in this MSKCC Institutional Review Board–approved retrospective chart review. All patients included were treated outside of previously reported prospective clinical trials [4,7]. All grade ≥3 nonhematologic toxicities, defined based on the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) 4.0, were recorded starting at the initiation of TBC conditioning and extending until 6 months post-transplantation. Three patients in our study cohort had less than 6 months of follow-up at the time of statistical analysis; however, these patients had no additional toxicities after the time of our analysis through 6 months post-transplantation. Clinically relevant grade ≥3 nonhematologic toxicities were defined as toxicities occurring at a frequency of ≥15% in all patients. Febrile neutropenia was not included as a clinically relevant nonhematologic toxicity for our analysis, given its expected prevalence with HDT-ASCT. Individual toxicities were categorized into organ system–based toxicity groups based on CTCAE 4.0 criteria, and related toxicity groups were combined in certain cases.

Baseline patient characteristics were assessed for association with more than the median number of clinically significant grade ≥3 nonhematologic toxicities using Fisher's exact test. Differences in the median number of grade ≥ 3 nonhematologic toxicities among each baseline pretransplantation patient characteristic were assessed using the Wilcoxon rank-sum test.

The TBC conditioning regimen comprised thiotepa 250 mg/m^2 i.v. on days –9, –8, and –7; busulfan 3.2 mg/kg i.v. on days –6, –5, and –4; and cyclophosphamide 60 mg/kg i.v. on days –3 and –2, with autologous stem cell infusion on day 0. In accordance with MSKCC's institutional ASCT guidelines, antiseizure prophylaxis with levetiracetam at 500 mg twice daily, either oral or i.v., was started 24 hours before the first dose of busulfan and continued through 24 hours after the last dose of busulfan. For 28 patients treated with PK-targeted busulfan between 2012 and 2015, PK analysis was done after the first dose, with predicted AUC reported based on 6-point kinetics. Dose adjustments based on PK values were made at the third busulfan dose. The target first-dose busulfan AUC was 4100 to 5200 umol*min/L, and the target total busulfan exposure was 12,300 to 15,600 umol*min/L. In accordance with MSKCC's institutional ASCT guidelines, antiviral prophylaxis with oral acyclovir 400 mg twice daily was started on admission, antibacterial prophylaxis for febrile neutropenia with oral ciprofloxacin 500 mg twice daily was started on day -2 and continued until engraftment, and antifungal prophylaxis with fluconazole 400 mg/day was started on admission and continued until engraftment. The associations between pre-transplantation characteristics with busulfan AUC and total busulfan exposure were assessed using the Wilcoxon rank-sum test. Progression-free survival (PFS) and overall survival (OS) for the entire cohort were estimated using the Kaplan-Meier (KM) method [13]. PFS was defined as the date of progression of disease or death from any cause, and OS was defined as date of death from any cause.

RESULTS

Baseline patient characteristics are detailed in Table 1 [14-16]. Of the 16 patients who underwent TBC-conditioned ASCT for SCNSL, 14 had secondary CNSL disease found at relapse, and 2 had secondary CNS disease at time of initial diagnosis. Two patients (5%) were HIV-positive before ASCT. The

Table 1
Baseline Pre-ASCT Characteristics

Characteristic	Value
Age, yr, median (range)	56 (25-71)
<60 yr, n (%)	31 (72)
≥60 yr, n (%)	12 (28)
Sex, n (%)	
Male	26 (60)
Female	17 (40)
KPS, median (range)	80 (70-90)
≥80, n (%)	41 (95)
<80, n (%)	2 (5)
HCT-CI, median (range)	3 (0-6)
>2, n (%)	22 (51)
≤2, n (%)	21 (49)
Disease, n (%)	
PCNSL	27 (63)
SCNSL	16 (37)
NHL histology, n (%)	
DLBCL	36 (84)
Other	7 (16)
CD34$^+$ dose, ×10^6 cells/kg, median (range)	4.64 (1.87-14.02)
Number of previous regimens, median (range)	2 (1-6)
≤2, n (%)	28 (65)
>2, n (%)	15 (35)
Previous treatments, n (%)	
R-MPV	30 (70)
HD-MTX	43 (100)
Ara-C	25 (58)
R-CHOP–like	15 (35)
Temozolomide	5 (12)
WBRT	9 (21)
History of IO/IT therapy	12 (28)
Status before ASCT, n (%)	
CR/CRu	35 (81)
PR	8 (19)

KPS, Karnofsky performance status; HCT-CI, Hematopoietic Cell Transplantation Comorbidity Index [14]; PCNSL, primary central nervous system lymphoma; SCNSL, secondary central nervous system lymphoma; NHL, non-Hodgkin lymphoma; DLBCL, diffuse large B cell lymphoma; R-MPV, rituximab/methotrexate/procarbazine/vincristine; HD-MTX, high-dose methotrexate, R-CHOP, rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone; WBRT, whole-brain radiotherapy; ASCT, autologous stem cell transplantation; CR, complete response; CRu, unconfirmed complete response; PR, partial response [15]; IO, intra-Ommaya; IT, intra-thecal.