Bendamustine Combined with Donor Lymphocytes Infusion in Hodgkin's Lymphoma Relapsing after Allogeneic Hematopoietic Stem Cell Transplantation

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Article history:
Received 3 April 2014
Accepted 23 May 2014

Key Words:
Hodgkin's lymphoma
Bendamustine
Allogeneic stem cell transplantation
Donor lymphocyte infusion

A B S T R A C T

The management of Hodgkin's lymphoma (HL) recurring after allogeneic stem cell transplantation is challenging. We retrospectively describe 18 adults treated with bendamustine followed by escalated donor lymphocyte infusion. Hematological toxicity was manageable (39% grade III to IV neutropenia and 28% grade III to IV thrombocytopenia). The overall response rate was 55%, with 3 complete and 7 partial responses. Median overall and progression-free survival were 11 (range, 1 to 52) and 6 (range, 1 to 28) months, respectively. One-year overall survival of responders (complete or partial) was 70% (95% confidence interval, 42% to 98%), although it was only 16% for nonresponders (n = 8). Our data show that bendamustine followed by donor lymphocyte infusion is feasible and can be efficacious as salvage treatment in HL relapsing after an allograft.

INTRODUCTION

Allogeneic stem cell transplantation (allo-SCT) is a conventional approach for patients with Hodgkin's lymphoma (HL) relapsing or refractory (rel/ref) to autologous hematopoietic stem cell transplantation [1-6]. However, the prognosis of advanced HL for patients undergoing allo-SCT remains poor, with an expected progression-free survival (PFS) ranging from 18% to 39%.

Management of patients relapsing after allo-SCT is not standardized and different approaches, such as reduction of immunosuppression, donor lymphocyte infusion (DLI), a second allogeneic SCT, and new drugs, including brentuximab vedotin, have been reported.

Bendamustine is an active agent in rel/ref HL patients, with a overall response rate (ORR) of 50% to 78% [7-10]. DLI in patients relapsing after allo-SCT induces a response rate (complete plus partial) in the 30% to 50% range and a median duration of 7.5 months [2,11]. Accordingly, we combined bendamustine and DLI in HL patients rel/ref after allo-SCT to synergistically provide reduction of tumor burden by chemotherapy followed by the antilymphoma activity of DLI. So far, this therapeutic option has been reported only in 2 patients [12]. We describe a cohort of 18 HL patients treated with bendamustine and DLI for HL rel/ref after allo-SCT.

PATIENTS AND METHODS

Over an 8-year period (2006 to 2013), we report on 18 adult patients with HL who experienced disease progression (PD) after a reduced-intensity conditioning followed by an unmanipulated allo-SCT and were considered eligible for salvage treatment with bendamustine followed by DLI (Table 1). Patients were treated after inclusion into a compassionate-use program and the provision of written informed consent. The median follow-up from relapse after allo-SCT was 310 days (range, 60 to 2939 days). Donor type was matched related sibling (n = 4), matched unrelated donor (MUD) (n = 2), and mismatched related donor (MMRD) (haploidentical donors n = 9; 7/10 HLA-match, n = 1; 8/10 HLA-match, n = 1; 9/10 HLA-match n = 1). Patients were treated in 2 centers in Milan, Italy: San Raffaele Hospital (patient no. 1 to 8) and Humanitas Cancer Center (patient no. 9 to 18). Patients were considered eligible for bendamustine when they had (1) performance status (Eastern Cooperative Oncology Group) ≤ 2; (2) no immunosoppression ongoing; and (3) no active infection. Patients were considered eligible for DLI after bendamustine in case of (1) absence of active graft-versus-host disease (GVHD), (2) no previous grade III to IV acute GVHD or severe chronic GVHD, and (3) no progression during bendamustine treatment. Bendamustine was administered at the dose of 120 mg/m^2 on days 1 and 2 of 28 days cycles. Eight patients treated at San Raffaele hospital received also rituximab (375 mg/m^2 on day 2 of each cycle) in combination with bendamustine [12-14]. Adequate hematopoietic recovery was required before each cycle (absolute neutrophil count $\geq$1000/μL; platelet count $\geq$75,000/μL) and treatment was delayed or eventually the dose was reduced if these criteria were not met.

Donor lymphocytes were collected by apheresis according to standard center protocol and the desired amount of CD3$^+$ donor T lymphocytes was infused after cytofluorimetric counting without any further manipulation. The initial dose of donor lymphocytes was $.5 \times 10^7$ CD3$^+$ T cells/kg of recipient's body weight (Humanitas Cancer Center) or 1×10^7 T cells/kg (San Raffaele Hospital), for patients who received a graft from a sibling donor and $.5 \times 10^6$ CD3$^+$ T cells/kg (Humanitas Cancer Center) or 1×10^6 CD3$^+$ T cells/kg (San Raffaele Hospital) in case of MUD or MMRD. DLI was given 5 to 10 days after each of 2 courses of bendamustine at one-half logarithmic dose escalation. After disease restaging, in the absence of complete remission (CR), limiting toxicities, grade III to IV acute GVHD or severe chronic GVHD, patients were treated with a second course of 2 cycles of bendamustine followed by one-half logarithmic dose escalated DLI up to 5×10^7 CD3$^+$ T cells/kg from a sibling donor or 5×10^6 CD3$^+$ T cells/kg from a MUD or MMRD. Kaplan-Meier estimates of overall survival (OS) were provided for all patients, starting from the first bendamustine cycle. Hazard ratio of mortality was calculated with Cox regression using response as a time-dependent variable.

RESULTS

Median age was 33 years (range, 21 to 48). Ann Arbor-Cotswold stage at relapse was III to IV in 16 of 18 patients.

Financial disclosure: See Acknowledgments on page 1447.

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1083-8791/$ – see front matter © 2014 American Society for Blood and Marrow Transplantation.
http://dx.doi.org/10.1016/j.bbmt.2014.05.024

Table 1
Patient's Characteristics

Patient No.	Sex/Age, yr	Hystotype, Stage	Disease Status at Allo-SCT	Donor Type, HLA Match	Conditioning Regimen	GVHD Prophylaxis	Time, SCT to Benda, d	No. of Cycles	No. of DLI	T Cell Dose/kg	aGVHD after DLI	cGVHD after DLI	Best Response after Benda [15]	Outcome and time from First Benda to Last Follow-up
# 1	M/41	MC-IV	PR	MUD 10/10	Treo-Flu-ATG	Rapa/MMF	330	1	0				PD	Dead (PD), 14 d
# 2	M/38	NS-IV	SD	MMRD 5/10	Treo-Flu-ATG	Rapa/MMF	525	6	1	1×10^6	IV	None	CR	Alive (PD), 19 mo
# 3	M/37	NS-IV	CR	MMRD 5/10	Treo-Flu-ATG	Rapa/MMF	453	2	0				PD	Dead (PD), 3 mo
# 4	M/44	NS-III	PR	MMRD 5/10	Treo-Flu-ATG	Rapa/MMF	225	4	0				SD	Dead (PD), 4 mo
# 5	F/44	Classic-IV	PR	MMRD 8/10	Treo-Flu-ATG	Rapa/MMF	272	5	2	1×10^6 (I) 5×10^6 (II)	0	Moderate (I) severe (II)	CR	Alive (PR), 40 mo
# 6	F/42	NS-IV	SD	MMRD 5/10	Treo-Flu-ATG	Rapa/MMF	334	6	1	1×10^6	0	Moderate	PR	Dead (infection), 12 mo
# 7	M/28	NS-III	PR	MMRD 9/10	Treo-Flu-ATG -TBI	Rapa/MMF	279	4	0				PR	Alive (CR after brentuximab) 14 mo
# 8	F/46	NS-III	CR	MMRD 5/10	Treo-Flu-ATG	Rapa/MMF	664	4	2	1×10^6 (I) 5×10^6 (II)	0 (I) IV (II)	None (I) NE (II)	CR	Dead (GVHD), 7 mo
# 9	M/29	NS-II	CR	MUD 10/10	Treo-Flu-ATG-TBI	Rapa/MMF	586	4	1	1×10^6	0	moderate	PR	Alive (PR), 12 mo
# 10	M/33	NS-IV	PR	MRD 10/10	Thio-Flu-CTX	CsA/MTX	120	1	1	$.5 \times 10^7$	0	none	PD	Dead (PD), 30 mo
# 11	M/36	NS-IV	PR	MRD 10/10	Thio-Mel-CTX	CsA/MTX	995	7	0				PR	Alive (CR after brentuximab) 45 mo
# 12	M/18	Classic-IV	SD	MRD 10/10	Flu-CTX	CsA	1456	9	3	$.5 \times 10^7$ (I) $.5 \times 10^7$ (II) 1×10^7 (III)	0	none	PR	Alive (CR after II allo-SCT) 53 mo
# 13	M/25	NS-IV	PR	MMRD 7/10	Flu-CTX-TBI	CTX/FK506/MMF	189	1	0				PD	Dead (PD), 5 mo
# 14	M/43	NS-IV	CR	MRD 10/10	Thio-Flu-CTX	CsA/MTX	399	7	3	$.5 \times 10^7$ (I) 1×10^7 (II) 5×10^7 (III)	0	none	PR	Alive (PD), 20 mo
# 15	M/24	NS-IV	CR	MMRD 5/10	Flu-CTX-TBI	CTX/FK506/MMF	613	2	0				PD	Alive (PD), 4 mo
# 16	F/34	MC-IV	CR	MMRD 5/10	Flu-CTX-TBI	CTX/FK506/MMF	133	6	2	$.5 \times 10^6$ (I) 1×10^6 (II)	0 (I) IV (II)	none	PR	Dead (GVHD), 7 mo
# 17	F/20	NS-IV	PR	MMRD 5/10	Flu-CTX-TBI	CTX/CsA/MMF	79	1	0				PD	Dead (PD), 22 d
# 18	M/31	NS-II	PD	MMRD 5/10	Thio-Flu-CTX-TBI	CTX/FK506/MMF	335	2	0				SD	Dead (PD), 12 mo

Benda indicates bendamustine; aGVHD, acute graft-versus-host disease; cGVHD, chronic graft-versus-host disease; M, male; MC, mixed cellularity; PR, partial response; Treo-Flu-ATG, treosulfan 42 g/m^2, fludarabine 150 mg/m^2, antithymocyte globulin Fresenius (ATG-Fresenius Neovii Biotech, Munich, Germany) 30 mg/kg, rituximab 500 mg; Rapa/MMF, rapamycine, mycophenolate mofetil; NS, nodular sclerosis; SD, stable disease; F, female; Treo-Flu-ATG-TBI, treosulfan 42 g/m^2, fludarabine 90 mg/m^2, antithymocyte globulin Fresenius (ATG-Fresenius Neovii Biotech) 30 mg/kg, total body irradiation 4 Gy; Thio-Flu-CTX, thiotepa 12 mg/kg, fludarabine 60 mg/m^2, cyclophosphamide 60 mg/kg; CsA/MTX, cyclosporin A and methotrexate; Thio-Mel-CTX, thiotepa 10 mg/kg, melphalan 60 mg/m^2, cyclophosphamide 100 mg/kg; Flu-CTX, fludarabine 60 mg/m^2 and cyclophosphamide 60 mg/kg; Flu-CTX-TBI, fludarabine 150 mg/m^2 and cyclophosphamide 30 mg/kg and total body irradiation 2 Gy; CTX/FK506/MMF, cyclophosphamide 50 mg/kg days +3 and +4 and FK506, mycophenolate mofetil; Thio-Flu-CTX-TBI, thiotepa 12 mg/kg and fludarabine 120 mg/m^2 and cyclophosphamide 30 mg/kg and total body irradiation 2 Gy.