International Blood Research & Reviews
2(4): 178-186, 2014, Article no. IBRR.2014.4.004

SCIENCEDOMAIN *international*
www.sciencedomain.org

Bendamustine for Relapsed and Refractory Hodgkin Lymphomas: Four Cases and a Review of the Literature

Semra Paydas[1*]

[1]*Department of Oncology, Cukurova University, Faculty of Medicine, Adana, Turkey.*

Author's contribution

This whole work was carried out by author SP.

Mini-review Article

Received 31st December 2013
Accepted 14th March 2014
Published 2nd May 2014

ABSTRACT

Aims: The management of relapsed/refractory Hodgkin lymphoma is challenging and new choices are needed. Brentuximab vedotin and bendamustine are two effective drugs in these cases. The aim of this study is to present the response to bendamustine after brentuximab failure.
Study Design: Retrospective study evaluating the response to bendamustine in four cases with relapsed or refractory Hodgkin lymphoma.
Place and Duration of Study: Cukurova University Faculty of Medicine Department of Oncology, between 2012 and 2014.
Methodology: Clinical and metabolic responses to bendamustine in four cases with relapsed refractory Hodgkin lymphoma were evaluated. Informed consent was obtained from the patients. Bendamustine was used in four cases with very refractory Hodgkin lymphoma after Brentuximab failure. The dosage was 120 mg/M2 for two consecutive days in 4 weeks, without growth factor support.
Results: Four cases with relapsed or refractory Hodgkin lymphoma were treated with bendamustine after brentuximab vedotin failure. Complete metabolic response was documented in two cases,one case did not respond and only short duration of response was determined in one case.
Conclusion: Bendamustine is an effective and cost-effective choice in cases with relapsed/refractory Hodgkin lymphoma after brentuximab vedotin failure. However response is of short duration and definitive treatment must be performed as soon as possible.

**Corresponding author: E-mail: sepay@cu.edu.tr;*

Keywords: Brentuximab vedotin; bendamustine; relapsed/refractory hodgkin lymphoma; stem cell transplantation.

ABBREVIATIONS

HL: Hodgkin lymphoma; HTB: high tumor burden; ABVD: doxorubicin-bleomycin-vinblastine-dacarbazine; DHAP: dexamethasone-cytosine arabinoside-cisplatin; ICE: ifosfamide-carboplatin-etoposide; GVP: gemcitabine-vinorelbine-prednisone; ESHAP: etoposide; VP-16: etoposide; Clb: chlorambucil; Vnb: vinorelbine; BV: brentuximab vedotin; B: bendamustine.

1. INTRODUCTION

Hodgkin lymphoma (HL) is one of the most curable malignant diseases in adults. However the disease becomes life threatening in cases which are refractory to primary treatment or which relapse after remission. Treatment failure is seen in about 20% of all cases and 30 to 35% of cases with advanced disease and unfavorable clinical features at presentation [1,2]. The standard of care in such cases is salvage chemotherapy and autologous stem cell transplantation. The critical factors are chemo-sensitivity and to obtain tumor-free stem cell collections [1]. However, cure has been reported in only half of these cases [1,3,4]. The most commonly used salvage regimens are BEAM (BCNU-etoposide-ara-C-melphalan), ICE (ifosfamide-carboplatin-etoposide), DHAP (dexamethasone-ara-C-cisplatin-), GDP (gemcitabine-dexamethasone-cisplatin), GND (gemcitabine-vinorelbine-liposomaldoxorubicin), MINE (mesna-ifosfamide-mitoxantrone-etoposide), and IEV (ifosfamide-etoposide-vinorelbine). Overall response rate with these salvage regimens is between 70 and 89% [4]. Transplant-related mortality is reported to be 2 to 9% [4]. On the other hand allogeneic stem cell transplantation is a potentially curable option but only a minority of cases are candidates for allogeneic transplantation [3,4]. Currently, optimal management of relapsed/refractory HL is controversial and novel agents play an important role in the management of these patients. Brentuximab vedotin is a new antibody drug conjugate approved for patients relapsing after autologous stem cell transplantation. FDA extended the indication of this drug for patients ineligible for transplantation and refractory to conventional chemotherapy combinations after objective responses were documented [5]. In recent years brentuximab vedotin has been accepted as a bridge for transplantation candidates not responding to standard treatments.

Bendamustine has been synthesized in 1963 in East Germany and after 44 years has been granted as drug in low grade lymphomas and chronic lymphocytic leukemia [6,7]. The activity of bendamustin in relapsed/refractory HL has been shown in phase II studies [8,9]. Here we reported four cases treated with bendamustine after brentuximab failure and we discussed the available data. Complete metabolic response was obtained in two cases.

2. CASES AND TREATMENT

Case 1: An 18-year-old woman with stage-I HL was treated with five cycles of ABVD (doxorubicin-bleomycin-vinblastine-dacarbazine). Relapse disease with B symptoms developed 86 months after diagnosis. Salvage treatment with DHAP was given and partial response was obtained. Autologous stem cells were collected but transplantation could not be performed due to social reasons. Six cycles of GVP (gemcitabine-vinorelbine-prednisolone), regimen was given after disease progression but the disease did not respond

to this regimen. Brentuximab vedotin was given for four cycles but PET/CT thereafter showed progression. ESHAP regimen as third salvage was given for subsequent progression. Ten years after first relapse bendamustine was given for 3 cycles, after which complete remission was seen on PET/CT. At the end of this therapy her condition was perfect and PET/CT showed complete response (Fig. 1). Transplantation was recommended and she was sent to transplant unit.

Case 2: A 25-year-old man with stage II-B HL involving sub-diaphragmatic sites was treated with six cycles of ABVD. Relapse developed 3 months after the end of chemotherapy. Three cycles of ICE chemotherapy was given as salvage therapy and autologous stem cell transplantation was performed. Four months later progression was seen and six cycles of GVP was given without response. After this failure, CCNU-etoposide-chlorambucil and prednisone combination was given with minimal response. A few months later, progression developed and everolimus was given for 6 months. There was initial slight clinical improvement but no objective response. Brentuximab vedotin was then given for four cycles but PET/CT showed progression. ESHAP was given with further progression. Bendamustine was given for 3 cycles without response after 6 years of posttransplant relapse. Lenalidomide 25mg daily was given for 3 months and did not respond and finally, etoposide-vinblastine-cytosine arabinoside and cisplatin containing regimen was started and he did not respond to this regimen. He died with septic shock.

Case 3: A 50-year-old man with stage II-B HL involving mediastinum and cervical lymph nodes was treated with six cycles of ABVD, complete remission determined. Relapse developed 3 months after the end of this treatment. ICE was given as salvage therapy and autologous stem cell transplantation was performed. Second relapse occurred 17 months with generalized lymph nodes and B symptoms after transplantation. Six cycles of GVP was given due to disease progression, partial response was achieved but one month later progression developed. Brentuximab vedotin was given for seven cycles; after 3 cycles there was partial response but progression developed. Bendamustine was given for 3 cycles. At the end of this therapy, PET/CT showed complete remission. Allogeneic transplantation was advised, but he refused. Bendamustine was completed to 6 cycles but at the end of this treatment relapse occurred and lenalidomide was planned.

Case 4: A 27-year-old woman with stage IV-B HL involving peritoneum, medistinum and retroperioneal lymph nodes was treated with six cycles of ABVD. At the end of this treatment complete remission was achieved but relapse developed two months later. Three cycles of DHAP was given as salvage therapy without response. Three cycles of GVP were given due to disease progression but the disease did not respond. Brentuximab vedotin was given for three cycles but PET/CT showed progression again. After 18 months of first diagnosis, bendamustine was given for 3 cycles. At the end of this therapy, PET/CT showed complete remission. The patient was referred for transplantation, but progression developed in colon 2 months after the last dose of bendamustine during pre-transplant procedures. Lenalidomide 25 mg daily was given for 3 months. PET CT showed progression again, bendamustine was re-started due to prior response. Table 1 shows the clinical outcome of these four cases.

Table 1. Clinical stage, age, gender, prior treatments of four cases treated with bendamustine

No of patient	Gender	Age	Age at diagnosis	Stage	Date of diagnosis	Follow up (Months)	First relapse from diag	Prior treatments	Transplantation
1	Female	30	18	I-HTB	January 2001	129	86	ABVDx5 DHAPx4 GVPx6 BVx4 ESHAPx3 Bx3	No
2	Male	31	25	II-B	May 2007	76	3	ABVDx6 ICEx3 GVPx6 CCNU-VP-16-Clb Everolimus BVx4 Bx3 Lenalidomide Ara-C-VP-16-CP-Vnb	Yes
3	Male	54	49	II-B	December 2008	54	3	ABVDx6 ICEx3 GVPx6 BVx7 Bx3	Yes
4	Female	30	27	IV-B	December 2010	33	1	ABVDx6 DHAPx3 GVPx3 BVx3 Bx3	No

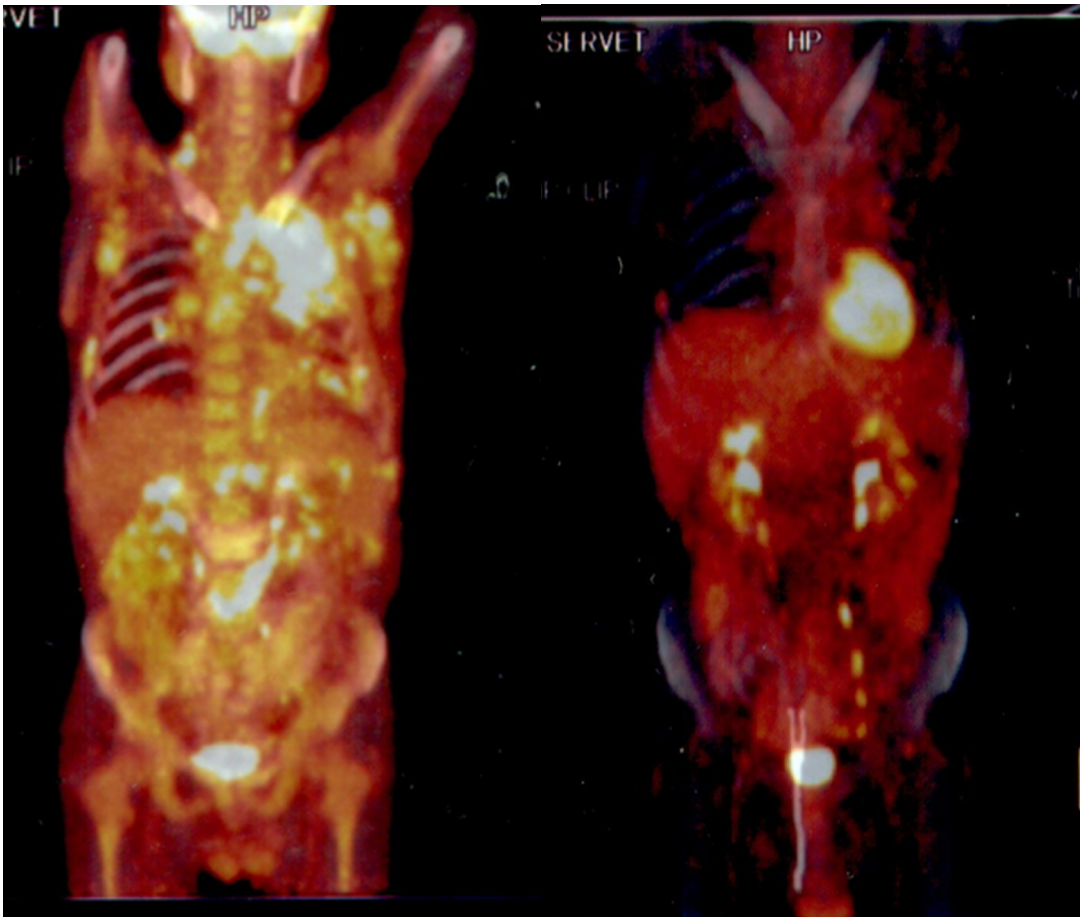

Fig. 1. PET CT before and after bendamustine in case 1

3. DISCUSSION

We reported bendumustine use in four cases which had not responded to brentuximab vedotin treatment. All cases had heavily pretreated HL. Two had received transplantation and had relapse at 3 and 17 months. These are heavily pretreated and they had very refractory disease. There are only two cases treated with bendamustine after brentuximab failure published by Zinzani et al. [10]. The responses obtained in these two cases and our four cases suggest that bendamustine is an important option in cases not responding to brentuximab vedotin or relapsing after response. Although our cases were heavily treated by various combinations, the drug was well tolerated by all patients and there was no delay due to hematologic or non-hematologic toxicity.

Bendamustine is a white, water-soluble microcrystalline powder with amphoteric property due to nitrogen mustard group and butyric acid side chain. Bendamustine has been used in combination with conventional anti-neoplastic drugs and in combination with monoclonal antibody rituximab, immune modulator drug lenalidomide and NF kappa B inhibitor bortezomib [12-14]. It has been suggested that bendamustine may be a candidate for combination with newer target based agents in addition to classic cytotoxics [8]. Another

important property of this drug is non cross-resistance with other conventional cytotoxic drugs such as cyclophosphamide, dacarbazine, anthracyclines, alkylating agents and etoposide [8,15,16]. Ongoing phase I-II clinical trials in relapsed refractory HL are NCT01412307 (lenalidomide-Bendamustine), NCT01535924 (gemcitabine-Bendamustine) [9]. Toxicity profile of Bendamustine is better compared with other cytotoxic drugs. Although grade III-IV neutropenia is seen in 40-60% of the cases, febrile neutropenia is seen in in only 7% of the cases and life threatening adverse effects are not seen [8,12,14,17]. An important side effect of this drug is the grade III-IV lymphocytopenia and is seen in 94% of the cases. There is no significant neurotoxicity despite extensive use in German Democratic Republic for more than 3 decades [12]. Bendamustine has important efficacy in cases with chronic lymphocytic leukemia, indolent and aggressive lymphomas, multiple myeloma and some solid tumors including small cell lung cancer and breast cancer [7]. Bendamustine efficacy in relapsed refractory Hodgkin lymphoma has been evaluated in phase II studies in relatively small number case series. In most of these studies bendamustine has been used in heavily treated cases and the majority of the cases had history of prior stem cell transplantation. Overall response rate and complete response rate have been found in 53-78 % and 29-38%, respectively [8,9,18]. Two important points in these studies are: 1. Outcomes were independent of disease chemo-sensitivity, previous stem cell transplantation and bendamustine dose intensity [8,9]. 2. Progression free survival was found to be relatively short and was around 5-6 months except in complete responders [8,9,19]. Another point is no response to bedamustine in cases who relapsed within 3 months of transplantation as seen in our second case [9]. Table 2. shows the response rates of conventional combination chemotherapies, small molecules, brentuximab vedotin and bendamustine in cases with relapsed/refractory HL.

Brentuximab vedotin is a CD30-directed antibody drug conjugate. Brentuximab vedotin is the most developed targeted treatment in HL targeting the CD30 receptor [20-22]. The safety and efficacy of brentuximab in combination with front-line and second-line regimens are being investigated in prospective and retrospective trials [5,10,23-25]. Overall response rate and complete response rate were 75 and 34%, respectively and progression free survival was 5.6 months in whole group and 20.5 months in complete responders. Best responses were seen after 3-4 cycles. Brentuximab had manageable toxicity profile and the most important toxicity is peripheral sensory neuropathy [23,26]. These studies suggest that brentuximab is a therapeutic bridge inducing a rapid response to allo or autologus transplant [26].

Table 2. Overal and complete response rates with different therapeutic choices in resistant refractory Hodgkin lymphoma

Regimen	Overall response rate (%)	Complete response rate (%)	Reference
Conventional chemotherapy combinations	70-89	17-76	1
Small molecules (HDAC inhibitors, everolimus, lenalidomide)	17-47	3-5	27
Brentuximab vedotin	30-88	10-50	23, 24
Bendamustine	53-78	29-38	8,18,19

It is very well known that microenvironment is very important in the biology of HL. HRS cells are rare in HL and these cells reside within in a microenvironment. For this reason targeting

intracellular signaling pathways and tumor microenvironment in addition to HRS cells are critical importance in the management of the disease [27]. So the combination brentuximab which targets HRS cells with molecules targeting signaling pathways like lenalidomide, m-TOR inhibitors, HDAC inhibitors may be more powerful. In addition to primary effects on tumor cells, bendamustine may be beneficial in HL by depleting the neoplastic microenvironment of tumor supporting T and B lymphocytes [28,29].

Another important point is the cost of these drugs. Three vials of brentuximab vedotin (3,333 €x3=9,999 €) or 4 vials of bendamustine (250 €x4=1000 €) are used for one cycle. Total one cycle cost is 10 fold expensive for brentixumab using when compared to bendamustine.

These results suggest that both brentuximab vedotin and bendamustine are feasible options in cases with relapsed refractory HL both candidates or non-candidates for stem cell transplantation. There are some critical points in these cases. Of course stem cell collection is critic in transplant receivers. Stem cell collection is not problem in brentuximab users while the effect of bendamustine on stem cell collection has not been carefully determined. However successful stem cell collections have been reported in cases treated with bendamustine in lymphoma trials [30]. Other important point is tumor volume before transplant which is an important predictor for transplantation rather than chemo-sensitivity [31]. For this reason maximal tumor de-bulking with brentuximab and/or bendamustine is very important in the management of relapsed refractory HL. Response duration is important, especially in candidates for allogeneic transplant and also in patients with non-candidates for transplant. At this point the combination of bendamustine and brentuximab may be important. Logic is to target HRS cells with brentuximab and to target the malignant cells and microenvironment with bendamustine via its cytotoxic and microenvironment effects. Toxicity profile is not problem in this combination, there is no overlapping toxic effects of these two drugs. Peripheral sensory neuropathy is the most important adverse effect of brentuximab while grade III-IV neutropenia is the adverse effect of bendamustine. Bendamustine plus brentuximab study (NCT01657331) is ongoing

4. CONCLUSION

Bendamustine may be an effective choice in cases with relapsed refractory HL not responding to brentuximab. One of the most critical point is who will be benefited from brentuximab and who from bendamustine. So far it has not been found a useful predictor at this matter. Identification of clinical and/or biological predictors for response to bendamustine or brentuximab is the key issue for this population**.**

CONSENT

Informed consent was obtained from the patients.

ETHICAL APPROVAL

Consent was obtained from health authotority.

ACKNOWLEDGEMENTS

Thanks for patients and their families for their consent

COMPETING INTERESTS

Author has declared that no competing interests exist.

REFERENCES

1. Holmberg MDL, Maloney DG. The role of autologous and allogeneic hematopoietic stem cell transplantation for Hodgkin lymphoma. J Natl Compr Canc Netw. 2011;9:1060–1071.
2. Bauer K, Skoetz N, Monsef I, Engert A, Brillant C. Comparison of chemotherapy including escalated BEACOPP versus chemotherapy including ABVD for patients with early unfavourable or advanced stage Hodgkin lymphoma. The Cochrane Database of Systematic Reviews, CD007941; 2011.
3. Brice P. Managing relapsed and refractory Hodgkin lymphoma. British Journal of Haematology. 2008;141:3–13.
4. Kuruvilla J, Keating A, Crump M. How I treat relapsed and refractory Hodgkin lymphoma Blood. 2011;117:4208-4217.
5. Lunning MA, Younes A. Brentuximab vedotin: The science of common sense. Leuk Lymphoma. 2013;54:2089–2090.
6. Alison J, Moskowitz AJ, Perales MA, et al. Outcomes for patients who fail high dose chemo radiotherapy and autologous stem cell rescue for relapsed and primary refractory Hodgkin lymphoma. Br J Haemat. 2009;146:158–163.
7. Gandhi V, Burger JA. Bendamustine in B cell malignancies: the new, 46-year old kid on the block. Clin Cancer Res. 2009;15:7456–7461.
8. Corazzelli G, Angrilli F, D'Arco A, et al. Efficacy and safety of bendamustine for the treatment of patients with recurring Hodgkin lymphoma. Br J Haemat. 2013;160:207–215.
9. Moskowitz AJ, Hamlin PA, Perales MA, et al. Phase II study of bendamustine in relapsed and refractory Hodgkin lymphoma. J Clin Oncol. 2012;31:456-460.
10. Zinzani PL, Derenzini E, Pellegrini C, Celli M, Broccoli A, Argnani L. Bendamustine efficacy in Hodgkin lymphoma patients relapsed/refractory to brentuximab vedotin. Br J Haematol; 2013.
11. Leoni LM, Hartley JA. Mechanism of action: The unique pattern of bendamustine-induced cytotoxicity semin hematol. 2011;48:12–23.
12. Montillo M, Ricci F, Tedeschi A, Vismara E, Morra E. Bendamustine: Perspective for an old drug in lymphoproliferative disorders. Expert Rev. Hematol. 2010;3:131–148.
13. Friedberg JW, Vose JM, Kelly JL, et al. The combination of bendamustine, bortezomib, and rituximab for patients with relapsed/refractory indolent and mantle cell non-Hodgkin lymphoma. Blood. 2011;117:2807-2812.
14. Cheson BD, Rummel MJ. Bendamustine: Rebirth of an old drug. J Clin Oncol. 2009; 27:1492-1501.
15. Leoni LM, Bailey B, Reifert J, et al. Bendamustine (Treanda) displays a distinct pattern of cytotoxicity and unique mechanistic features compared with other alkylating agents. Clin Cancer Res. 2008;14:309-317.
16. Leoni LM, Bailey B, Reifert J: SDX-105 (Bendamustine), a clinically active antineoplastic agent posesses a unique mechanism of action. Blood. 2003;102:640. (abstr 2363).

17. Friedberg JW, Cohen P, Chen L, et al. Bendamustine in patients with rituximab-refractory and alkylator-refractory, indolent, and transformed non-Hodgkin's lymphoma: Results from a phase II multicenter single-agent study. J Clin Oncol. 2008; 26:204-210.
18. Moskowitz AJ, Hamlin PA, Gerecitano J. Bendamustine is highly active in heavily Pre-treated relapsed and refractory hodgkin lymphoma and serves as a bridge to allogeneic stem cell transplant. Blood. 2009;114:Abstract 720.
19. D'Elia MG, De Angelis F, et al. Efficacy of bendamustine as salvage treatment in an heavily pretreated Hodgkin lymphoma. Leukemia Research. 2010;34:300–301.
20. Francisco JA, Cerveny CG, Meyer DL, et al. cAC10-vcMMAE, an anti-CD30-monomethyl auristatin E conjugate with potent and selective antitumor activity. Blood. 2003;102:1458–1465.
21. Doronina SO, Toki BE, Torgov MY, et al. Development of potent monoclonal antibody auristatin conjugates for cancer therapy. Nature Biotech. 2003;21:778–784.
22. Zheng B, Fiumara P, Li YV, et al. MEK/ERK pathway is aberrantly active in Hodgkin disease: A signaling pathway shared by CD30, CD40, and RANK that regulates cell proliferation and survival. Blood. 2003;102:1019–1027.
23. Younes A, Gopal AK, Smith SE, et al. Results of a pivotal phase II study of Brentuximab vedotin for patients with relapsed or refractory Hodgkin's lymphoma. J Clin Oncol. 2012;30:2183-2189.
24. Rothe A, Sasse S, Goergen H, et al. Brentuximab vedotin for relapsed or refractory CD30+hematologic malignancies: The German Hodgkin Study Group experience. Blood. 2012;120:1470-1472.
25. Gibb A, Jones C, Bloor A, Kulkarni S, Illidge T, Linton K, Radford J. Brentuximab vedotin in refractory CD30+ lymphomas: A bridge to allogeneic transplantation in approximately one quarter of patients treated on a named patient programme at a single UK center. Haematologica. 2013;98:611-614.
26. Zinzani PL, Viviani S, Anastasia A, et al. Brentuximab vedotin in relapsed/refractory Hodgkin's lymphoma: The Italian experience and results of its use in daily clinical practice outside clinical trials. Haematologica. 2013;98:1232-1236.
27. Dinner S, Advani R. Targeted therapy in relapsed classical Hodgkin lymphoma. J Natl Compr Canc Netw. 2013;11:968-976 .
28. Aldinucci D, Gloghini A, Pinto A, De Filippi R, Carbone A. The classical Hodgkin's lymphoma microenvironment and its role in promoting tumour growth and immune escape. Journal of Pathology. 2010;221:248–263.
29. Steidl C, Connors JM, Gascoyne RD. Molecular pathogenesis of Hodgkin's lymphoma: Increasing evidence of the importance of the microenvironment. J Clin Oncol. 2011; 29:1812–1826.
30. Brugger W, Ghielmini M. Patient management bendamustine in indolent Non-Hodgkin's lymphoma: A practice guide for patient management the oncologist. The Oncologist published online July 30; 2013.
31. Lim ABM, Ritchie DS. Hodgkin lymphoma, allogeneic transplantation and the graftversus-tumor effect: size does matter. Just Accepted by Leukemia & Lymphoma DOI: 10.3109/10428194.2013.848438.

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sciencedomain.org/review-history.php?iid=491&id=28&aid=4438