World Journal of Stem Cells

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4252/wjsc.v7.i7.1039

World J Stem Cells 2015 August 26; 7(7): 1039-1046
ISSN 1948-0210 (online)

MINIREVIEWS

Advancement in high dose therapy and autologous stem cell rescue in lymphoma

Alessandro Isidori, Cristina Clissa, Federica Loscocco, Barbara Guiducci, Sara Barulli, Lara Malerba, Elisa Gabucci, Giuseppe Visani

Alessandro Isidori, Cristina Clissa, Federica Loscocco, Barbara Guiducci, Sara Barulli, Lara Malerba, Elisa Gabucci, Giuseppe Visani, Haematology and Haematopoietic Stem Cell Transplant Center, AORMN, 61100 Pesaro, Italy

Author contributions: Isidori A, Clissa C and Loscocco F contributed equally to this work, generated the tables and wrote the manuscript; all authors contributed to the concept, drafting, revising and final editing of this manuscript; Visani G made critical revisions related to important intellectual content of the manuscript.

Conflict-of-interest statement: The authors declare no competing financial interests.

Correspondence to: Alessandro Isidori, MD, PhD, Haematology and Haematopoietic Stem Cell Transplant Center, Marche Nord Hospital, Via Lombroso, 61100 Pesaro, Italy. asidori@gmail.com
Telephone: +39-721-364022
Fax: +39-721-364026

Received: November 25, 2014
Peer-review started: November 26, 2014
First decision: January 8, 2015
Revised: May 18, 2015
Accepted: July 16, 2015
Article in press: July 19, 2015
Published online: August 26, 2015

Abstract

Although advanced stage aggressive non-Hodgkin's lymphomas and Hodgkin's disease are thought to be chemotherapy-responsive cancers, a considerable number of patients either relapse or never attain a remission. High-dose therapy (HDT) followed by autologous stem cell transplantation (ASCT) is often the only possibility of cure for most of these patients. However, many controversial issues still remain with respect to HDT/ASCT for lymphomas, including its role for, the optimal timing of transplantation, the best conditioning regimen and the potential use of localized radiotherapy or immunologic methods to decrease post-transplant recurrence. Recently, mainly due to the unavailability of carmustine, several novel conditioning protocols have been clinically developed, with the aim of improving the overall outcome by enhancing the anti-lymphoma effect and, at the same time, by reducing short and long-term toxicity. Furthermore, the better safety profiles of novel approaches would definitively allow patients aged more than 65-70 years to benefit from this therapeutic option. In this review, we will briefly discuss the most relevant and recent data available regarding HDT/ASCT in lymphomas.

Key words: Hodgkin lymphoma; Non-Hodgkin lymphoma; High dose therapy; Autologous stem cell transplantation; New drugs

Core tip: High-dose therapy (HDT) followed by autologous stem cell transplantation (ASCT) is considered the golden standard for the vast majority of patients with both Hodgkin and non-Hodgkin lymphoma, who either relapse or never attain a remission. However, several questions about HDT/ASCT still remain unanswered, also comprising, but not limited to, its role in newly diagnosed patients with advanced stage disease. The incorporation of novel drugs in both salvage and conditioning regimens has recently

revitalized the HDT/ASCT area, with several phase I-II trials performed during the last 5 years. This review will focus on the most recent data regarding HDT/ASCT in lymphomas.

Isidori A, Clissa C, Loscocco F, Guiducci B, Barulli S, Malerba L, Gabucci E, Visani G. Advancement in high dose therapy and autologous stem cell rescue in lymphoma. *World J Stem Cells* 2015; 7(7): 1039-1046 Available from: URL: http://www.wjgnet.com/1948-0210/full/v7/i7/1039.htm DOI: http://dx.doi.org/10.4252/wjsc.v7.i7.1039

INTRODUCTION

High-dose therapy (HDT) followed by autologous stem cell transplant (ASCT) is the therapy of choice for patients with chemosensitive, aggressive, relapsed non-Hodgkin lymphoma, basing on the results of the PARMA and CORAL study (NHL)[1,2]. Moreover, HDT/ASCT is considered the standard of care for hodgkin lymphoma (HL) patients in chemosensitive relapse[3]. Different HDT regimens followed by ASCT are able to produce rates of disease-free survival (DFS) and overall survival (OS) of approximately 30% to 70%. Despite HDT/ASCT prolonged DFS, few major drawbacks still limit the utility of this approach for a wide patient population. As an example, the introduction of Rituximab in every-day clinical practice has dramatically reduced the number of patients addressed to HDT/ASCT, specially in front-line therapy. Up to now, no regimen was demonstrated to be superior to another in randomized trials[4]. Therefore, novel strategies are urgently required. As a consequence, and due to the sudden unavailability of carmustine, the International Investigators have developed novel HDT/ASCT protocol in resistant/relapsed aggressive NHL or HD within the last 5 years, aiming to improve the outcome while reducing toxicity. In this paper, we will discuss the data emerging from few recent clinical trials testing HDT/ASCT in aggressive lymphomas.

CONDITIONING REGIMENS PRE-ASCT IN LYMPHOMAS

High dose chemotherapy and ASCT is the standard of care for patients with recurrent HL and NHL who fail immunochemotherapy upfront, improving long-term survival in 30% to 50%. Several factors impact on survival of lymphoma patients after HDT/ASCT. In this regard, the most important predictive factor is disease status at transplant (chemosensitive *vs* chemoresistant). Nevertheless, transplant related morbidity and mortality still remain relevant in influencing the outcome of the transplant procedure. Therefore, when planning an autologus transplant, the efficacy of HDT to eradicate residual disease after salvage therapy may be well balanced with toxicity to normal tissues, in order to maximize the probabilities of the procedure of being successful. Despite the efforts made to further increase the therapeutic window of new high-dose regimens, at present we do not have an evidence that clearly demonstrates the superiority of a specific HDT regimen to the others.

BEAM (carmustine, etoposide, cytarabine, melphalan) regimen is considered the regimen of choice for patients with HL and NHL submitted to ASCT, due to its acceptable safety profile and a quite high antitumor efficacy. The transplant related mortality (TRM) of the BEAM regimen is quite low, depending mainly on disease status at transplant, infectious history and prior lines of therapy. Early, non-hematological toxicities of carmustine, such as nausea, vomiting, mucositis, hepatotoxicity, diarrhea and nephrotoxicity are well known, and worldwide Clinicians know how to manage them. However, late toxicities are still a matter of concern, in particular second tumor and interstitial non-infectious pneumonitis, which have been reported in 16%-64% of patients receiving carmustine-based conditioning regimens, being fatal in approximately 9% of the patients.

Accordingly, various scientists and cooperative groups still continue in this search for the holy Grail, focusing mainly on the incorporation of novel drugs, radioimmunoconjugates, monoclonal antibodies and/or other stimuli for the immunologic system during the early pre- and post- transplantation phases.

Hodgkin lymphoma

The results of the most important trials with HDT/ASCT in HD are listed in Table 1.

Ramzi *et al*[5] reported the results of non-cryopreserved ASCT of 45 HL patients receiving an alternative CEAM regimen in which iv carmustine was substituted by oral lomustine (CCNU: 2 chloroethyl cyclohexyl nitrosourea). Forty-five relapsed/refractory HL patients underwent conditioning regimen with: lomustine 200 mg/m^2 on day-3, etoposide 1000 mg/m^2 on day-3 and day-2, cytarabine 1000 mg/m^2 on day-3 and day-2, melphalan 140 mg/m^2 on day-1. All 45 patients showed engraftment of infused stem cell. Grade 2 and grade 3 mucositis was seen in 64.5% of patients. TRM at 100 d was 2.2%. Median DFS was 20 mo (range: 4-60 mo). After a follow up of more than 2-year, the 2-year DFS in 30 evaluable patients was 77% and the 2-year OS was 84% (25/30 patients).

Czyz *et al*[6] have retrospectively evaluated the efficacy of a modified BEAM regimen followed by ASCT in 132 patients relapsed/refractory HL patients. The 10-year OS and progression free survival (PFS) were 76% and 66%, respectively. Age > 45 years, more than one salvage regimens and chemoresistant disease at transplant were all predictive for poor OS in multivariate analysis.

In 2011 Shafey *et al*[7] have retrospectively evaluated 73 patients with refractory/relapsed HL treated in a 15 year period with a double high-dose therapy consisting

Table 1 High dose therapy followed by autologous stem cell transplantation in Hodgkin lymphoma

Ref.	Year	Patients (*n*)	Status of HL	Regimen	TRM (%)	PFS (%)	OS (%)	Follow-up (mo)
Ramzi *et al*[5]	2012	45	R/R	CEAM	2.2	77	84	24
Czyz *et al*[6]	2013	132	R/R	Modified BEAM	-	66	76	68
Shafey *et al*[7]	2012	73	R/R	DICEP	1	61	80	56
Sinha *et al*[9]	2013	30	R/R	VTEPA	0	67	81	32
Di Ianni *et al*[10]	2012	58	R/R	TECA	0	72	82	60

HL: Hodgkin lymphoma; DICEP: Dose-intensive cyclophosphamide, etoposide, cisplatin; VTEPA: Vinorelbine, paclitaxel, etoposide and cisplatin; TECA: Thiotepa, etoposide and carboplatin; R/R: Relapsed/refractory; OS: Overall survival; PFS: Progression free survival.

of dose intensified cyclophosphamide, etoposide and cisplatin reinduction, followed by high-dose melphalan and ASCT. TRM was 1%. The 5-year PFS and OS rates were 61% and 80%, respectively. In multivariate analyses, response to reinduction therapy and DICEP and International Prognostic System score at relapse were the only factors independently predicting PFS and OS.

As already stated, the standard of care for refractory or relapsed HL patients is a salvage therapy followed by HDT/ASCT. However, patients whit chemoresistant disease after salvage therapy have a small probabilities of achieving a long lasting response and a long overall survival. In 2006, the Emory Univesity group tested in a phase I study, the combination of cytarabine with fixed doses of vinorelbine, paclitaxel, etoposide and cisplatin (VTEPA) as second salvage therapy in patients with resistant/relapsed lymphoma , showing an overall response rate (ORR) of 33%[8]. In 2013 the same group further examined the effectiveness of VTEPA in 30 patients with relapsed/refractory HL[9]. Among 27 evaluable patients, ORR was 70% (7 CR, 12 PR). All but 1 responding patients (66%) subsequently underwent ASCT. This therapeutic strategy (VTEPA + ASCT) produced a median PFS and OS of 28 and 38 mo from transplant, respectively.

In 2012 Di Ianni *et al*[10], reported their experience with a novel HDT regimen including thiotepa, etoposide and carboplatin (TECA) in HL patients. From March 1999 to December 2005, 58 patients with primary refractory or relapsed were enrolled in a phase Ⅱ study. The conditioning regimen consisted of etoposide (250 mg/m^2 days 1-4), thiotepa (166 mg/m^2 days 2-4) and carboplatin (266 mg/m^2 days 2-4). After salvage therapy, 46 patients had chemosensitive disease (30 CR + 16 PR), whereas 12 were chemoresistant. At transplantation, 30 patients were in CR, 16 in PR and 12 showed a chemoresistance to salvage chemotherapy. TRM was 0%. The global ORR was 79.3% (37 CR, 7 PR), but 12 patients still did not respond to therapy neither after HDT/ASCT. The 5-year DFS and OS were superior for relapsed patients with respect to primary refractory ones. After 5-year of follow-up, approximately 75% of patients were alive. Even if the idea of combining thiotepa with more conventional drugs was interesting, the results of this study are in line with other trials, given the high percentage (80%) of chemosensitive patients at transplant. Hard-to-respond, chemoresistant patients (12/58, 20%) did not show any benefit from the thiotepa-containing regimen.

Non-Hodgkin lymphoma

The results of the most relevant studies with HDT/ASCT in NHL are listed in Table 2.

As for HL, the standard salvage therapy of relapsed/refractory aggressive NHL mainly relies on HDT/ASCT, hopefully in patients with chemosensitive disease. Nevertheless, reaching of long lasting DFS remains not easy.

Kim *et al*[11] reported the results of a novel NEAM regimen, administered prior to ASCT, to 69 patients with resistant/relapsed NHL. The NEAM regimen, another, novel variant of the standard BEAM, consisted of mitoxantrone (12 mg/m^2 *iv* on day-6 to day-4), etoposide (100 mg/m^2) and cytarabine (100 mg/m^2 iv every 12 h from day-6 to day-3), melphalan (single 140 mg/m^2 dose at day-2). TRM at day-100 was 2.9%. Median event free survival (EFS) was 17.9 mo, whereas estimated 2-year OS was 64.2%.

In 2012 Falzetti *et al*[12] reported the results of the TECA (thiotepa, etoposide and carboplatin) regimen administered to 45 patients with NHL at various disease stage. TRM was 4.4%. The ORR was 77.8% (30 CR, 5 PR). Ten patients (22.2%) did not respond. The mean 5-year OS was 71.1%. Patients with low (1) International prognostic index (IPI) ad diagnosis had a better ORR and 5-year OS were than for those with intermediate IPI (2 and 3).

Another strategy to increase efficacy of the conventional BEAM regimen is to add novel drugs in a new reinforced BEAM combo. In this regard, the University of Nebraska Medical Center group designed a phase Ⅰ/Ⅱ trial testing the safety and the efficacy of the addition of a proteasome inhibitor to standard BEAM prior to ASCT in resistant/relapsed indolent or transformed NHL (including T cell lymphomas) or mantle-cell lymphoma (MCL, only in first CR)[13]. Patients received 4 doses of escalating bortezomib (0.8, 1, 1.3, 1.5 mg/m^2) on day-11, day-8, day-5 and day-2 prior to ASCT. After the maximum tolerated dose (MTD, 1 mg/m^2) was defined, other 20 patients entered the phase II to determine a preliminary ORR, PFS and OS with this regimen. As a whole, 42 (13 + 29) patients were enrolled. Non-hematologic side effects were

Table 2 High dose therapy followed by autologous stem cell transplantation in non-Hodgkin lymphoma

Ref.	Year	Patients (*n*)	Disease	Regimen	TRM (%)	ORR (%)	OS (%)	Follow-up (mo)
Kim *et al*[11]	2012	44	Chemosensitive-NHL	NEAM	2.9	79	64	24
Falzetti *et al*[12]	2012	45	HR NHL	TT-Vp-Car	4.4	77	71	60
William *et al*[13]	2014	42	R/R NHL	V-BEAM	0	87	91	12
Visani *et al*[14]	2011	43	R/R HL and NHL	BeEAM	0	82	81	18
Visani *et al*[15]	2014	43	R/R HL and NHL	BeEAM	0	72	88	41
Isidori *et al*[16]	2014	37	R/R NHL	BeEAM	2.7	88	94	9
Musso *et al*[17]	2010	84	R/R HL and NHL	FEAM	2.4	73	88	13
Kruger *et al*[19]	2012	16	R/R NHL	RIT + BEAM	6	94	75	44
Winter *et al*[20]	2009	44	R/R NHL	Z-BEAM	2.2	77	60	33
Shimoni *et al*[21]	2012	43	R/R NHL	Z-BEAM	0	97	91	24
Briones *et al*[22]	2014	30	R/R NHL	RIT + BEAM	3.5	70	63	31

HL: Hodgkin lymphoma; RIT: Radioimmunotherapy; BeEAM: Bendamustine, etoposide, ara-C, melphalan; FEAM: Fotemustine plus etoposide, cytarabine and melphalan; NEAM: Mitoxantrone, etoposide, cytarabine, and melphalan; NHL: Non-Hodgkin lymphoma; R/R: Relapsed/refractory; OS: Overall survival; TT-Vp-Car: Thiotepa, Vepeside, carmustine; V-BEAM: Velcade plus standard BEAM.

comparable to those observed with other regimen, with the relevant exception of an increase in grade Ⅲ peripheral neuropathy, related to the use of bortezomib, and in grade Ⅲ gastrointestinal toxicity. TRM at day 100 was 0%. At 1 year after ASCT, 38 patients were evaluable for response; 32 (84%) were in CR and 1 (3%) was in PR, resulting in an impressive ORR of 87%. these results were better among patients treated in the phase Ⅱ, for whom ORR was 89% (84% CR, 5% PR). PFS was 83% at 1 year and 32% at 5 years. OS was 91% at 1 year and 67% at 5 years. The authors performed also an exploratory analysis to determine whether this regimen was more effective in a given histological pattern, finding no statistical difference. Conversely, by comparing the results of bortezomib-BEAM with standard BEAM in an historic cohort of patients matched for histology at their Institution, the authors showed an advantage in both PFS and OS at 5 years for MCL patients (57% and 72% *vs* 43% and 50%, respectively), even if not statistically significant. Even if promising, in particular in MCL patients, the bortezomib-BEAM regimen discourages, due to the lack of an evident benefit and higher than expected toxicity, its further exploration in a randomized, phase Ⅲ study.

In 2011 Visani *et al*[14] reported the efficacy of increasing doses of bendamustine (160 mg/m^2, 180 mg/m^2 and 200 mg/m^2 given on day-7 and day-6) in addition to fixed doses of etoposide, cytarabine and melphalan (BeEAM regimen) administered as preparative regimen to ASCT. Forty-three patients with resistant/relapsed HL (n = 15) and NHL (n = 28) were enrolled, 9 in the phase Ⅰ and 34 in the phase Ⅱ study. No patients experienced dose limiting toxicity. TRM at day 100 was 0%. The follow-up period at the time of publication was 18 mo, with 81% being alive and disease-free at that time. Disease type (HL *vs* NHL) and disease status at transplant (chemosensitive *vs* chemoresistant) significantly influenced DFS. Interestingly, the authors updated their experience in 2014[15], reporting a 72% PFS at 3 years, that allowed them to met the primary end-point of the study. Median PFS and OS were still not reached. Disease status at transplant (chemosensitive *vs* chemoresistant) was still a stron predictor of outcome. Conversely, disease type (HL *vs* NHL) was no longer affecting PFS nor OS[15].

By riding the same wave, Isidori *et al*[16] recently reported the preliminary data of a phase Ⅱ study to confirm the effectiveness of BeEAM as a preparative regimen for autologous stem cell transplantation in resistant/relapsed aggressive B-cell non-Hodgkin lymphoma patients. Thirty-seven patients (median age 56 years, range 19-69) with resistant/relapsed aggressive B-cell NHL were enrolled, up to now, in the study. Briefly, 27 patients had advanced stage disease (Ⅲ-Ⅳ), 12 were primary refractory and 25 had relapsed. Thirty-three patients had good performance status (WHO 0-1), and 11 patients presented with 1 or more relevant comorbidities (range: 1-5). Nineteen patients were in Ⅱ or subsequent CR after salvage therapy, whereas 16 were in PR and 2 had progressive disease. All patients engrafted, with a median time to ANC > 0.5 x 10^9/L of 10 d. TRM at day-100 was 2.7%. Eight out of 37 patients presented a fever of unknown origin (21.6%), whereas 19 patients (51%) presented a clinically documented infection. One patient died due to an incomplete hematological recovery after transplant, producing an overall transplant related mortality of 2.7%. Twenty-seven out of 37 patients are evaluable up to now for response: 22/27 (81.5%) obtained a CR, 2/27 a PR, resultin in an ORR of approximately 90%. After a median follow-up of 9 mo from transplant (range 2-24), 5/24 patients relapsed, whereas 19/24 (79.1%) are still alive, in continuous CR. The Authors concluded that the BeEAM regimen preliminary confirmed its safety and its promising efficacy in resistant-relapsed aggressive B-cell lymphomas.

In 2010 Musso *et al*[17] substituted carmustine with the chloroethylnitrosurea fotemustine (150 mg/m^2 on day-7 and day-6) in the standard BEAM (FEAM regimen). 84 resistant/relapsed HL and NHL patients were enrolled in this study. Non-hematological side effects were superimposable to those of the BEAM regimen, with 7 patients experiencing grade 4 mucositis, without any other relevant grade 4 toxicity. TRM at day-100

was 2.4%. Even if the FEAM HDT regimen showed a favorable safety profile, it is not possible to draw any conclusion regarding survival or long-term efficacy due to the short follow-up period of 17-mo sonly.

Another question that still remains unanswered is related to the relative efficacy of HDT/ASCT in NHL patient population treated with chemoimmunotherapy comprising rituximab front-line. As a fact, this is really a burning question, as all patients with B cell malignancies are treated upfront, at present, with anti-CD20 monoclonal antibody plus chemotherapy. Nevertheless, the utility of HDT/ASCT for NHL patients in first CR is still a matter of great debate.

Recently, the Southwest Oncology Group tried to answer, at least partly, this question by conducting a large, randomized trial testing HDT/ASCT as consolidation therapy, in comparison to standard chemoimmunotherapy[18]. 397 patients were enrolled, and 370/397 received five cycles of CHOP with (47%) or without (53%) rituximab. Responding patients (CR + PR) were subsequently randomized to receive 3 other cycles CHOP ± Rituximab (control group) or one additional cycle of CHOP ± Rituximab followed by ASCT (transplantation group), conditioned with standard BEAM regimen or total body irradiation (12 Gy). The primary efficacy end points were 2-year PFS and OS. Of 370 induction-eligible patients, 253 were randomly assigned to the transplantation group (125) or the control group (128). Like many of the randomized trials and several meta-analysis, this study showed an improvement in PFS for the combined high-risk and high-intermediate risk who are chemosensitive to induction therapy. However, again and again, this study was not able to demonstrate, in randomized fashion, an advantage in OS for HDT/ASCT, neither for high risk patients[18]. On the other hand, we have to keep in mind that 29% of patients who had a relapse or progression after standard therapy, were rescued with HDT/ASCT, resulting in a relevant bias for the analysis of a statistical OS benefit for HDT/ASCT over the control group. Finally, the study was not designed and powered to address subgroup-related question, and therefore any point in favor of HDT/ASCT for high risk patients is merely speculative.

The incorporation of new drugs into HDT regimen prior to ASCT in B-cell lymphomas has recently been helped by the development of radioimmunotherapy (RIT). The potential advantage of using radioimmunoconjugates, with or without chemotherapy, prior to ASCT, relies on the opportunity of delivering localized radiation therapy to the site of tumor. This allows to minimize the toxicity of total body irradiation, with the goal of decreasing relapse rate without adding toxicity to the conditioning regimen. At present, no study comparing RIT and standard radiation therapy has been done. However, few preliminary phase Ⅱ studies with RIT as a part of a preparative regimen have produce encouraging results by showing a high safety profile, a low TRM and a preliminary efficacy.

Kruger *et al*[19] enrolled 16 patients with resistant/relapsed NHL in a phase Ⅱ study testing ^{131}I-rituximab-BEAM and ASCT. A single dose of ^{131}I-rituximab was given on day-15, whereas standard BEAM started on day-6 prior to ASCT. Non hematological side effects were mild in grade, without any grade Ⅳ toxicity. All patients engrafted, with a 0% TRM at day-100. Results were encouraging, with 75% of patients being alive and disease free after a median follow-up of 44 mo from ASCT (range 4-108). Interestingly, each patient received only a limited whole body radiation of only 0.75 Gy.

Winter *et al*[20] conducted a phase Ⅰ-Ⅱ study in 44 patients with resistant/relapsed NHL, by adding yttrium-90 (^{90}Y) ibritumomab tiuxetan to standard BEAM and ASCT (Z-BEAM regimen). A significant proportion of patients (30%) entering the study had chemoresistant disease after salvage therapy. Non hematological toxicities were similar to those reported with standard BEAM. Two dose limiting toxicities occurred at 17 Gy dose level, which made 15 Gy the recommended dose for the phase Ⅱ of the study. After a median observation time of 33 mo, the estimated 3-year PFS and OS were 43% and 60%, respectively. When looking at these results, it has to keep in mind the significant proportion of chemoresistant patients, who perform extremely poor with conventional HDT regimen.

Shimoni *et al*[21] randomized 43 patients with CD20 positive aggressive B-cell lymphoma to receive either Z-BEAM (n = 22) or standard BEAM (n = 21). Ibritumomab tiuxetan was administered at 0.4 mCi/kg on day-14 prior to ASCT. Non hematological toxicities were mild and comparable within the 2 groups. TRM at day-10 was 0% in both groups. As a whole, Z-BEAM did not show a significant advantage in OS with respect to standard BEAM. However, there was a trend in 2-year PFS and OS in favor of Z-BEAM (59% and 91% *vs* 37% and 62%, respectively. The Authors speculated that Z-BEAM could be superior to standard BEAM for patients receiving frontline chemoimmuotherapy containing Rituximab. However, the sample size of the study was very small, and the statistical analysis did not allow to draw any conclusion regarding the superiority of a regimen to another.

Another study with yttrium-90 Ibritumomab tiuxetan was conducted and published by Spanish Group in 2013[22]. It was a prospective, multicenter, phase Ⅱ clinical trial which enrolled 30 patients with induction failure or refractory B-cell NHL. Patients received ^{90}Y-ibritumomab tiuxetan at a fixed dose of 0.4 mCi/kg, 14 d prior to the BEAM chemotherapy. Non hematological toxicities were similar to those reported with standard BEAM, and TRM at day-100 was 0%. Intriguingly, the vast majority of patients (25/30) underwent to HDT/ASCT with chemoresistant disease. Therefore, this regimen produce an outstanding ORR of 70%, with 60% of patients obtaining a CR; estimated 3-year PFS and OS were 61% and 63%, respectively, and the median time of observation for surviving

patients was 31 mo. The Authors enthusiastically concluded that ^{90}Y-ibritumomab tiuxetan based HDT regimen prior to ASCT results in a terrific response rate, with promising survival in a group of refractory lymphoma patients with extremely poor prognosis.

Taken together, these results are in favor of RIT-based HDT regimen prior to ASCT, given the good toxicity profile and the promising efficacy. However, none of these studies was able to demonstrate a statistical benefit for the RIT-based HDT, probably also due to the small sample size of the trials. In conclusion, a large, randomized trial comparing RIT-BEAM and standard BEAM is warranted before drawing any conclusion and before recommending the use of RIT-HDT outside from controlled clinical trials.

With regards to T-cell lymphomas, the use of HDT/ASCT is still considered an "experimental" practice. In fact, only a small amount of prospective trials evaluating the impact of HDT/ASCT as consolidation of first-line therapy have been reported up to now[23-25]. Even if the results coming from these studies suggest an improve in both DFS and OS when compared with chemo alone[23-25], an important amount of patients is not able to perform frontline transplant, principally due to disease progression during induction chemotherapy, thus underlying the need for a better induction regimen. In relapsed T-cell lymphomas, HDT/ASCT produced results similar to those obtained in relapsed, aggressive B-cell lymphomas. Reported long-term DFS approaches 30% to 50%, making HDT/ASCT a valuable option in the therapeutic armamentarium for this indication. Conversely, the use of HDT/ASCT in refractory T-cell lymphoma produce extremely poor outcome, and other strategies could be preferred for this setting of patients. In conclusion, we think that there is room for HDT/ASCT as a part of first-line treatment, especially in responding patients. On the other hand, resistant or relapsed patients may be better addressed to allogeneic transplantation or to clinical trials.

Late complications of HDT followed by ASCT in lymphomas

Late complications among HL survivors are still a matter of concern. Several papers have reported high rates of second cancers, heart disease, pulmonary fibrosis, and infections[26]. The recognition of these risks has resulted in modification of chemotherapy regimens and of radiation fields and doses[26,27]. HDT/ASCT by itself is also affected by late *sequelae* of treatment, but specific data for the HL population are limited[26,27]. Few studies identified predictors of post-transplant long-term quality of life specifically for patients with HL, who have higher rates of treatment-related late morbidity and mortality than patients with other cancer diagnoses[26,27].

The most relevant study that evaluated the risk of late morbidity and mortality, among patients with relapsed/refractory HL after HDT and ASCT was performed by the MSKCC group[28]. this study, conducted on 153 HL patients treated with HDT/ASCT between 1985 and 1998 who survived $\geqslant$ 2 years after ASCT, demonstrated a risk ratio of second malignancy equal to 6.5 (95%CI: 3.6-10.7) when compared with the general population, but limited to 2.4 (95%CI: 1.4-4.05) when compared with patients with HL[28]. In other words, the risk of developing a second tumor after HDT/ASCT was elevated if compared with the cancer risk in the general population, but was less pronounced when compared with patients with HL in SEER registry[29].

Data on NHL are quite similar, demonstrating a higher risk of developing a second malignancy mostly for patients receiving TBI as a part of the preparative regimen to ASCT. However, to the best of our knowledge, large studies have not been conducted in this patient population.

Our guess is that, in the era of the TBI-free conditioning regimens, what really counts for the development of a second malignancies or a late effect (*e.g.,* cardiomyopathy) in lymphoma patients, is mainly the type and the dose of chemo- and radiation therapy performed before transplant, and only in a minimal extent HDT/ASCT.

CONCLUSION

High dose therapy followed by autologous stem cell transplantation has still a major role in the treatment of resistant/relapsed HL and NHL. The relevant advancements made with the incorporation of novel drugs and/or radioimmunoconjugates into preparative regimens translated in a higher PFS rate with respect to the historical standards. Furthermore, TRM and overall toxicities seem to be lower. However, data on the possible overall survival advantage given by the novel agents are still controversial, and probably only large, randomized phase Ⅲ trials could pick a winner between the plethora of new drugs recently incorporated in novel conditioning regimens. Our personal experience with Bendamustine, used both in Phase Ⅱ trials and everyday clinical practice, indicate the favorable safety profile of the BeEAM regimen, coupled with a relevant efficacy in a hard-to-treat population of resistant/relapsed lymphoma patients.

A different scenario could be represented by maintenance therapy with new drugs, such as Brentuximab Vedotin in HL or Ibrutinib or Lenalidomide in aggressive NHL, in patients chemoresistant who obtain at least a PR after HDT/ASCT. In this setting of patients, the use of a drug with a different mechanism of action and a manageable safety profile could help the physician in the path to cure of a highly resistant subpopulation of lymphoma patients.

REFERENCES

1 **Philip T**, Guglielmi C, Hagenbeek A, Somers R, Van der Lelie H, Bron D, Sonneveld P, Gisselbrecht C, Cahn JY, Harousseau JL. Autologous bone marrow transplantation as compared with salvage

chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. *N Engl J Med* 1995; **333**: 1540-1545 [PMID: 7477169 DOI: 10.1056/NEJM199512073332305]

2 **Gisselbrecht C**, Glass B, Mounier N, Singh Gill D, Linch DC, Trneny M, Bosly A, Ketterer N, Shpilberg O, Hagberg H, Ma D, Brière J, Moskowitz CH, Schmitz N. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. *J Clin Oncol* 2010; **28**: 4184-4190 [PMID: 20660832 DOI: 10.1200/JCO.2010.28.1618]

3 **Linch DC**, Winfield D, Goldstone AH, Moir D, Hancock B, McMillan A, Chopra R, Milligan D, Hudson GV. Dose intensification with autologous bone-marrow transplantation in relapsed and resistant Hodgkin's disease: results of a BNLI randomised trial. *Lancet* 1993; **341**: 1051-1054 [PMID: 8096958 DOI: 10.1016/0140-6736(93)92411-L]

4 **Oliansky DM**, Larson RA, Weisdorf D, Dillon H, Ratko TA, Wall D, McCarthy PL, Hahn T. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the treatment of adult acute lymphoblastic leukemia: update of the 2006 evidence-based review. *Biol Blood Marrow Transplant* 2012; **18**: 18-36.e6 [PMID: 21803017 DOI: 10.1016/j.bbmt.2010.07.008]

5 **Ramzi M**, Mohamadian M, Vojdani R, Dehghani M, Nourani H, Zakerinia M, Haghighinejad H. Autologous noncryopreserved hematopoietic stem cell transplant with CEAM as a modified conditioning regimen in patients with Hodgkin lymphoma: a single-center experience with a new protocol. *Exp Clin Transplant* 2012; **10**: 163-167 [PMID: 22432762 DOI: 10.6002/ect.2011.0092]

6 **Czyz A**, Lojko-Dankowska A, Dytfeld D, Nowicki A, Gil L, Matuszak M, Kozlowska-Skrzypczak M, Kazmierczak M, Bembnista E, Komarnicki M. Prognostic factors and long-term outcome of autologous haematopoietic stem cell transplantation following a uniform-modified BEAM-conditioning regimen for patients with refractory or relapsed Hodgkin lymphoma: a single-center experience. *Med Oncol* 2013; **30**: 611 [PMID: 23702734 DOI: 10.1007/s12032-013-0611y]

7 **Shafey M**, Duan Q, Russel J, Duggan P, Balogh A, Stewart DA. Double high-dose therapy with dose-intensive cyclophosphamide, etoposide, cisplatin (DICEP) followed by high dose melphalan and autologous stem cell transplantation for relapsed/refractory Hodgkin lymphoma. *Leuk and Lymphoma* 2012; **53**: 596-602 [DOI: 10.3109/10428194.2011.624227]

8 **Lonial S**, Arellano M, Hutcherson D, Langston A, Flowers C, Heffner LT, Winton E, Jo Lechowicz M, Waller EK. Results of a clinical phase I dose-escalation study of cytarabine in combination with fixed-dose vinorelbine, paclitaxel, etoposide and cisplatin for the treatment of relapsed/refractory lymphoma. *Leuk Lymphoma* 2006; **47**: 2155-2162 [PMID: 17071490 DOI: 10.1080/10428190600774923]

9 **Sinha R**, Shenoy PJ, King N, Lechowicz MJ, Bumpers K, Hutcherson D, Arellano M, Langston A, Kaufman J, Heffner LT, Waller EK, Nooka A, Flowers CR, Lonial S. Vinorelbine, paclitaxel, etoposide, cisplatin, and cytarabine (VTEPA) is an effective second salvage therapy for relapsed/refractory Hodgkin lymphoma. *Clin Lymphoma Myeloma Leuk* 2013; **13**: 657-663 [PMID: 24094894 DOI: 10.1016/2013.05.007]

10 **Di Ianni M**, Ballanti S, Iodice G, Reale A, Falzetti F, Minelli O, Serio G, Martelli MF, Dammacco F, Vacca A, Ria R. High-dose thiotepa, etoposide and carboplatin as conditioning regimen for autologous stem cell transplantation in patients with high-risk Hodgkin's lymphoma. *Hematology* 2012; **17**: 23-27 [PMID: 22549444 DOI: 10.1179/102453312X13221316477534]

11 **Kim JW**, Lee HJ, Yi HG, Kim BS, Bang SM, Kim JS, Kim I, Yoon SS, Lee JS, Kim CS, Park S, Kim BK. Mitoxantrone, etoposide, cytarabine, and melphalan (NEAM) followed by autologous stem cell transplantation for patients with chemosensitive aggressive non-Hodgkin lymphoma. *Am J Hematol* 2012; **87**: 479-483 [PMID: 22388671 DOI: 10.1002/ajh.23150]

12 **Falzetti F**, Di Ianni M, Ballanti S, Iodice G, Reale A, Minelli O, Serio G, Martelli MF, Dammacco F, Vacca A, Ria R. High-dose thiotepa, etoposide and carboplatin as conditioning regimen for autologous stem cell transplantation in patients with high-risk non-Hodgkin lymphoma. *Clin Exp Med* 2012; **12**: 165-171 [PMID: 21928053 DOI: 10.1007/s10238-011-0157-2]

13 **William BM**, Allen MS, Loberiza FR, Bociek RG, Bierman PJ, Armitage JO, Vose JM. Phase I/II study of bortezomib-BEAM and autologous hematopoietic stem cell transplantation for relapsed indolent non-Hodgkin lymphoma, transformed, or mantle cell lymphoma. *Biol Blood Marrow Transplant* 2014; **20**: 536-542 [PMID: 24434781 DOI: 10.1016/j.bbmt.2014.01.004]

14 **Visani G**, Malerba L, Stefani PM, Capria S, Galieni P, Gaudio F, Specchia G, Meloni G, Gherlinzoni F, Giardini C, Falcioni S, Cuberli F, Gobbi M, Sarina B, Santoro A, Ferrara F, Rocchi M, Ocio EM, Caballero MD, Isidori A. BeEAM (bendamustine, etoposide, cytarabine, melphalan) before autologous stem cell transplantation is safe and effective for resistant/relapsed lymphoma patients. *Blood* 2011; **118**: 3419-3425 [PMID: 21816830 DOI: 10.1182/blood-2011-04-351924]

15 **Visani G**, Stefani PM, Capria S, Malerba L, Galieni P, Gaudio F, Specchia G, Meloni G, Gherlinzoni F, Gonella R, Gobbi M, Santoro A, Ferrara F, Rocchi M, Ocio EM, Caballero MD, Loscocco F, Isidori A. Bendamustine, etoposide, cytarabine, melphalan, and autologous stem cell rescue produce a 72% 3-year PFS in resistant lymphoma. *Blood* 2014; **124**: 3029-3031 [PMID: 25377565 DOI: 10.1182/blood-2014-08-596668]

16 **Isidori A**, Olivieri A, Angelucci E, Capria S, Angrilli F, Castagnari B, Vallisa D, Fattori P, mengarelli A, Patriarca F, Galieni P, Gaudio F, Scalzulli P, Tosi P, Montanari M, Baronciani D, Falorio S, Meloni G, Zaccaria A, Cascavilla N, Loscocco F, Rocchi M, Visani G. High dose therapy with bendamustine, etoposide, ara-C, melphalan (BeEAM) prior to autologous stem cell transplant is safe and effective in aggressive B-cell non Hodgkin lymphoma: an Italian phase II, multicenter study. *Haematologica* 2014; **99**: s27

17 **Musso M**, Scalone R, Marcacci G, Lanza F, Di Renzo N, Cascavilla N, Di Bartolomeo P, Crescimanno A, Perrone T, Pinto A. Fotemustine plus etoposide, cytarabine and melphalan (FEAM) as a new conditioning regimen for lymphoma patients undergoing auto-SCT: a multicenter feasibility study. *Bone Marrow Transplant* 2010; **45**: 1147-1153 [PMID: 19898504 DOI: 10.1038/bmt.2009.318]

18 **Stiff PJ**, Unger JM, Cook JR, Constine LS, Couban S, Stewart DA, Shea TC, Porcu P, Winter JN, Kahl BS, Miller TP, Tubbs RR, Marcellus D, Friedberg JW, Barton KP, Mills GM, LeBlanc M, Rimsza LM, Forman SJ, Fisher RI. Autologous transplantation as consolidation for aggressive non-Hodgkin's lymphoma. *N Engl J Med* 2013; **369**: 1681-1690 [PMID: 24171516 DOI: 10.1056/NEJMoa13101077]

19 **Kruger PC**, Cooney JP, Turner JH. Iodine-131 rituximab radioimmunotherapy with BEAM conditioning and autologous stem cell transplant salvage therapy for relapsed/refractory aggressive non-Hodgkin lymphoma. *Cancer Biother Radiopharm* 2012; **27**: 552-560 [PMID: 23062193 DOI: 10.1089/cbr.2012.1275]

20 **Winter JN**, Inwards DJ, Spies S, Wiseman G, Patton D, Erwin W, Rademaker AW, Weitner BB, Williams SF, Tallman MS, Micallef I, Mehta J, Singhal S, Evens AM, Zimmer M, Molina A, White CA, Gordon LI. Yttrium-90 ibritumomab tiuxetan doses calculated to deliver up to 15 Gy to critical organs may be safely combined with high-dose BEAM and autologous transplantation in relapsed or refractory B-cell non-Hodgkin's lymphoma. *J Clin Oncol* 2009; **27**: 1653-1659 [PMID: 19255322 DOI: 10.1200/JCO.2008.19.2245]

21 **Shimoni A**, Avivi I, Rowe JM, Yeshurun M, Levi I, Or R, Patachenko P, Avigdor A, Zwas T, Nagler A. A randomized study comparing yttrium-90 ibritumomab tiuxetan (Zevalin) and high-dose BEAM chemotherapy versus BEAM alone as the conditioning regimen before autologous stem cell transplantation in patients with aggressive lymphoma. *Cancer* 2012; **118**: 4706-4714 [PMID: 22252613 DOI: 10.1002/cncr.27418]

22 **Briones J**, Novelli S, García-Marco JA, Tomás JF, Bernal T, Grande C, Canales MA, Torres A, Moraleda JM, Panizo C, Jarque I, Palmero F, Hernández M, González-Barca E, López D, Caballero D. Autologous stem cell transplantation after conditioning with yttrium-90 ibritumomab tiuxetan plus BEAM in refractory non-Hodgkin diffuse large B-cell lymphoma: results of a prospective,

multicenter, phase II clinical trial. *Haematologica* 2014; **99**: 505-510 [PMID: 24162789 DOI: 10.3324/haematol.2013.093450]

23 **Corradini P**, Tarella C, Zallio F, Dodero A, Zanni M, Valagussa P, Gianni AM, Rambaldi A, Barbui T, Cortelazzo S. Long-term follow-up of patients with peripheral T-cell lymphomas treated up-front with high-dose chemotherapy followed by autologous stem cell transplantation. *Leukemia* 2006; **20**: 1533-1538 [PMID: 16871285 DOI: 10.1038/sj.leu.2404306]

24 **Reimer P**, Rüdiger T, Geissinger E, Weissinger F, Nerl C, Schmitz N, Engert A, Einsele H, Müller-Hermelink HK, Wilhelm M. Autologous stem-cell transplantation as first-line therapy in peripheral T-cell lymphomas: results of a prospective multicenter study. *J Clin Oncol* 2009; **27**: 106-113 [PMID: 19029417 DOI: 10.1200/JCO.2008.17.4870]

25 **d'Amore F**, Relander T, Lauritzsen GF, Jantunen E, Hagberg H, Anderson H, Holte H, Österborg A, Merup M, Brown P, Kuittinen O, Erlanson M, Østenstad B, Fagerli UM, Gadeberg OV, Sundström C, Delabie J, Ralfkiaer E, Vornanen M, Toldbod HE. Up-front autologous stem-cell transplantation in peripheral T-cell lymphoma: NLG-T-01. *J Clin Oncol* 2012; **30**: 3093-3099 [PMID: 22851556 DOI: 10.1200/JCO.2011.40.2719]

26 **Fernandez HF**, Escalón MP, Pereira D, Lazarus HM. Autotransplant conditioning regimens for aggressive lymphoma: are we on the right road? *Bone Marrow Transplant* 2007; **40**: 505-513 [PMID: 17589535 DOI: 10.1038/sj.bmt.175744]

27 **Hodgson DC**. Late effects in the era of modern therapy for Hodgkin lymphoma. *Hematology Am Soc Hematol Educ Program* 2011; **2011**: 323-329 [PMID: 22160053 DOI: 10.1182/asheducation-2011.1.323]

28 **Isidori A**, Piccaluga PP, Loscocco F, Guiducci B, Barulli S, Ricciardi T, Picardi P, Visani G. High-dose therapy followed by stem cell transplantation in Hodgkin's lymphoma: past and future. *Expert Rev Hematol* 2013; **6**: 451-464 [PMID: 23991931 DOI: 10.1586/17474086.2013.814451]

29 **Goodman KA**, Riedel E, Serrano V, Gulati S, Moskowitz CH, Yahalom J. Long-term effects of high-dose chemotherapy and radiation for relapsed and refractory Hodgkin's lymphoma. *J Clin Oncol* 2008; **26**: 5240-5247 [PMID: 18809615 DOI: 10.1200/JCO.2007.15.5507]

P- Reviewer: Jun Y, Kiselev SL **S- Editor**: Tian YL
L- Editor: A **E- Editor**: Wu HL

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com