bjh research paper

Effect of the dose per body weight of conditioning chemotherapy on severity of mucositis and risk of relapse after autologous haematopoietic stem cell transplantation in relapsed diffuse large B cell lymphoma

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Summary

High-dose chemotherapy and haematopoietic stem cell (HSC) transplantation is considered standard therapy in patients with chemosensitive relapsed diffuse large B cell lymphoma (DLBCL). BCNU (carmustine), etoposide, cytarabine and melphalan (BEAM) is a widely used standard DLBCL conditioning regimen. The practice of basing chemotherapy doses on body surface area (BSA) is empirical and the best biometric parameter to dose chemotherapy is unknown. Weight-based dosing has been suggested to better predict toxicity of the conditioning regimen. We correlated the dose/weight ratio with toxicity and overall outcome in a uniform cohort of 80 consecutive patients receiving HSC transplant for relapsed DLBCL at Mayo Clinic, Rochester, MN following BSA-dosed BEAM conditioning chemotherapy. Melphalan dose was used as surrogate for the entire regimen. Median age at the time of transplant was 62 (26–77) years; 65% were males. The median melphalan dose was 3·2 mg/kg (range 2·2–4·5). Patients who received >3·6 mg/kg of melphalan were more likely to have grade 3 or 4 mucositis (44·4% vs. 9·8%, $P = 0{\cdot}001$) and prolonged hospitalization (median 13 vs. 7 d; $P = 0{\cdot}04$). Dose/weight ratio did not correlate with cumulative incidence of relapse ($P = 0{\cdot}3$) or survival ($P = 0{\cdot}8$). Transplant physicians should consider limiting the dose of BEAM to the equivalent of 3·6 mg/kg of melphalan.

Keywords: lymphoma, large B-cell, diffuse, stem cell transplantation, chemotherapy, mucositis, body surface area.

Diffuse large B cell lymphoma (DLBCL) is the most common type of lymphoma worldwide (The Non-Hodgkin's Lymphoma Classification Project, 1997). Although most patients now achieve a complete response after treatment with modern chemoimmunotherapy (Feugier *et al*, 2005; Habermann *et al*, 2006; Pfreundschuh *et al*, 2006), relapses are still common. Relapsed DLBCL carries a very poor prognosis and is usually fatal in the absence of haematopoietic stem cell (HSC) transplantation (Velasquez *et al*, 1988; Philip *et al*, 1995; Gutierrez *et al*, 2000).

A landmark randomized trial (Philip *et al*, 1995) and the experience of multiple phase II trials (Vose *et al*, 1993; Prince *et al*, 1996) have consolidated autologous HSC transplantation as the preferred therapeutic option for patients with relapsed DLBCL and chemosensitive disease. Although many total body irradiation (TBI) and non-TBI based conditioning regimens have been employed, the combination of BCNU (carmustine), etoposide, cytarabine and melphalan (BEAM) (Gaspard *et al*, 1988; Caballero *et al*, 1997) is considered the standard conditioning regimen for autologous transplantation in lymphomas. The toxicity profile of BEAM is predictable and more favorable than alternative regimens (Puig *et al*, 2006), making transplantation feasible even in elderly patients with comorbidities (Buadi *et al*, 2006).

Chemotherapy dosing is traditionally based on body surface area (BSA), often calculated by employing the corrected ideal

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body weight. There is little, if any, evidence that BSA is the best biometric parameter on which to base chemotherapy doses (Page *et al*, 1988; Gurney, 2002). As a consequence of the use of BSA, low-weight patients receive higher per-weight doses of chemotherapy with a potential increase in toxicity. Whether the higher dose/weight ratio in these patients affects the relapse rate is unknown and to limit the doses of chemotherapy administered to a certain dose/weight ratio would probably create a concern for higher risk of relapse.

Mucositis is one of the most important complications of autologous transplantation and is implicated in prolonged hospitalization, prolonged use of narcotics and occurrence of opportunistic infections (Sonis *et al*, 2001; Peterson & Cariello, 2004; Grazziutti *et al*, 2006; Blijlevens *et al*, 2008). In autologous HSC transplant for multiple myeloma (Grazziutti *et al*, 2006; Blijlevens *et al*, 2008) and, most recently, DLBCL (Blijlevens *et al*, 2008), mucositis has been associated with dose/weight ratio of conditioning chemotherapy.

We analyzed a comprehensive database of uniformly treated and assessed patients undergoing BEAM conditioning for autologous HSC transplantation at a single institution to correlate dose/weight with occurrence and severity of mucositis, length of hospitalization and risk of relapse after transplantation.

Methods

HSC transplantation

All patients included in this analysis had provided informed consent to undergo autologous HSC transplantation and to have their de-identified information used for research purposes. The present analysis was approved by the Institutional Review Board of the Mayo Clinic, Rochester, MN.

We reviewed the database containing all autologous transplantations for Non-Hodgkin lymphomas performed at the Mayo Clinic Rochester, MN between 2001 and 2006. In order to enter the analysis, patients had to fulfill the following eligibility criteria: age $\geq$ 18 years, confirmed diagnosis of DLBCL, anthracycline-based first line therapy, achievement of at least an unconfirmed complete response (CRu) after first line therapy and chemosensitive relapse (at least partial response (PR) to salvage chemotherapy). There was no upper age limit. Only patients conditioned with BEAM (BCNU (carmustine) 300 mg/m^2 on day -6; etoposide 200 mg/m^2 per day divided in two daily doses on days -5 to -2; cytarabine 200 mg/m^2 per day divided in two daily doses on days -5 to -2 and melphalan 140 mg/m^2 on day -1) were included. For all patients whose actual weight (AW) was higher than the ideal body weight (IBW), the corrected ideal body weight (cIBW) was used to calculate the BSA. For males we used the equation IBW (kg) = 50 + 2·3 $\times$ (height in inches $-$ 60) and for females IBW (kg) = 45 + 2·3 $\times$ (height in inches $-$ 60). For both genders we used cIBW = 0·25 $\times$ (AW$-$IBW) + IBW.

Procedures for HSC mobilization, harvesting and infusion, supportive care measures and criteria for engraftment have been presented elsewhere (Costa *et al*, 2008). None of the patients were treated with recombinant human (rh) keratinocyte growth factor (rhKGF, Palifermin) or rh fibroblast growth factor-20 (rhFGF-20, Velafermin). For each of the patients we extracted demographic data (age, gender), biometric (weight, height) and disease-related data (number and type of regimens received, prior use of rituximab, disease status at the time of transplantation). Transplant-specific information, including engraftment data and grading of toxicity had been prospectively obtained and entered in the database. Of specific interest, mucositis had been prospectively graded using the National Cancer Institute (NCI) common toxicity criteria version 2.0 (CTC 2.0) grading system (http://ctep.cancer.gov/forms/CTCv20_4-30-992.pdf). Prospectively captured mucositis grading was confirmed by review of individual charts. Number of days spent in the hospital in the first 30 d after transplantation was retrospectively extracted from electronic charts.

The outcome of each patient was obtained from the database or by reviewing individual electronic charts and consisted of information regarding occurrence and timing of relapse and occurrence, timing and cause of death.

Statistics

In order to evaluate the effect of conditioning chemotherapy dose/weight on the occurrence and severity of mucositis, the duration of hospitalization and risk of relapse, melphalan was chosen as the surrogate for dose intensity in the entire regimen. As the doses of all drugs were based on the same biometric parameter (BSA), the choice of surrogate drug would not affect the results. For each patient, the ratio between dose of melphalan given and actual body weight was calculated allowing patients to be allocated in the upper quartile, middle half of lower quartile of dose/weight ratio group. All subsequent comparisons were made among these three groups regarding frequency and severity of mucositis, duration of hospital stay, disease relapse and survival.

Cumulative incidence of relapse (CIR) and overall survival (OS) were calculated from the transplant day until the day the event (relapse or death) was documented. The CIR curve was generated using the complement of Kaplan and Meier method. Comparisons of time variables between groups were made using log-rank analysis. Chi-square statistics was used for comparisons between proportions while the non-parametric Mann–Whitney *U* test was used for comparisons between numeric distributions. All statistic tests used a significance level of $<0{\cdot}05$.

Results

Characteristics of the cohort

Eighty patients met the eligibility criteria and entered the present analysis. The median age of patients undergoing

Table I. Patient characteristics.

	n (%)
Age (years)	
≤49	14 (18)
50–59	20 (25)
60–69	31 (39)
≥70	15 (19)
Males/females	52 (65)/28 (35)
Prior exposure to rituximab	62 (78)
Rituximab with first therapy	38 (47)
Number of prior chemotherapy regimens	
2	71 (89)
3	7 (9)
4	2 (3)
Disease status at the time of transplant	
CR or CRu	26 (33)
PR	54 (67)

CR, complete response; CRu, unconfirmed complete response; PR, partial response.

transplantation was 62 years (range 26–77 years) and 65% were male (Table I). Most patients (89%) had received two prior chemotherapy regimens, with at least one of the regimens containing rituximab in 78% of cases. All patients had at least a partial response to the last chemotherapy regimen administered before transplantation. Details on the overall outcome of this cohort have been reported elsewhere (Costa *et al*, 2008).

Conditioning dose/weight and toxicity

Median dose of melphalan was 3·2 mg/kg (range 2·2–4·5 mg/kg; Fig 1) and, as expected, melphalan dose/actual weight decreased with higher BSA. Twenty-three patients were in the lower quartile of melphalan dose/weight ratio (<2·9 mg/kg), 38 in the middle half (2·9–3·6 mg/kg) and 19 in the upper quartile (>3·6 mg/kg).

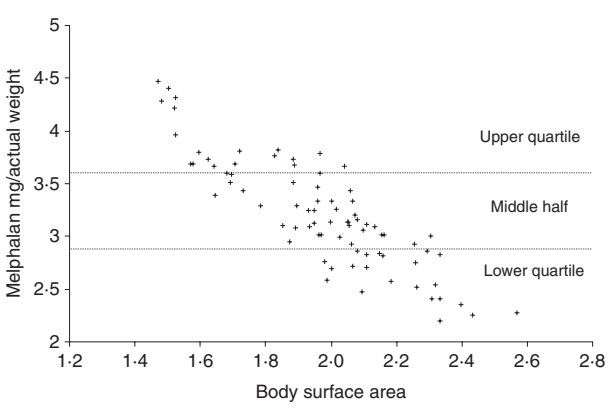

Fig 1. Scatterplot of melphalan dose/kg ratio and BSA showing the decrease in dose/kg ratio with increasing BSA.

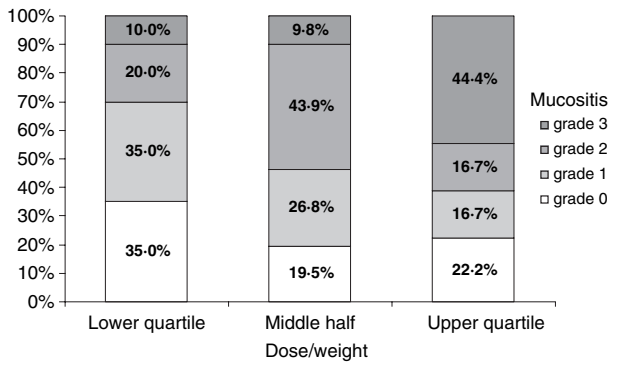

Fig 2. Incidence and grading of mucositis according to melphalan dose/kg (P = 0·001 for upper quartile vs. remaining).

Mucositis grading was available for 79 of the 80 patients and had not been prospectively extracted in one patient. There was an increase in the occurrence and severity of mucositis with higher melphalan dose/weight (Fig 2). In fact, the rate of severe mucositis (grade > 2) was significantly higher in the upper quartile of melphalan dose/weight (>3·6 mg/kg) than in the remaining groups (44·4% vs. 9·8%; P = 0·001).

At Mayo Clinic Rochester, MN, autologous transplantation was conducted primarily on an outpatient basis and patients were hospitalized only when their requirements exceeded the routine need for laboratory and clinical monitoring, growth factors administration, transfusion of blood products and empirical antibiotic therapy for fever prior to engraftment. In this setting, the number of days spent in the hospital during the first 30 d after transplantation served as a good surrogate for overall toxicity of the procedure. We found that patients in the upper quartile of Melphalan dose/weight spent a median of 13 (range 0–30) days in hospital while the remaining patients spent 7 (0–24) days in the hospital (Fig 3; P = 0·04). Although 8/19 patients (42%) in the upper quartile of dose/weight spent more than two weeks in the hospital, only seven out of the 61 (11%) remaining patients had prolonged hospitalization (P = 0·003).

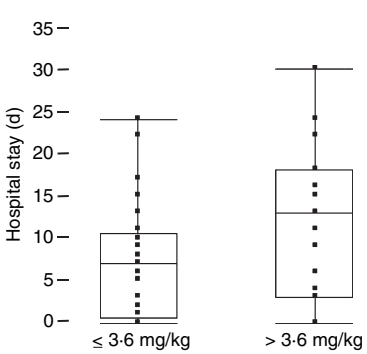

Fig 3. Duration of hospital stay for patients in the upper quartile of melphalan dose/kg and remaining patients (P = 0·04 for upper quartile vs. remaining).

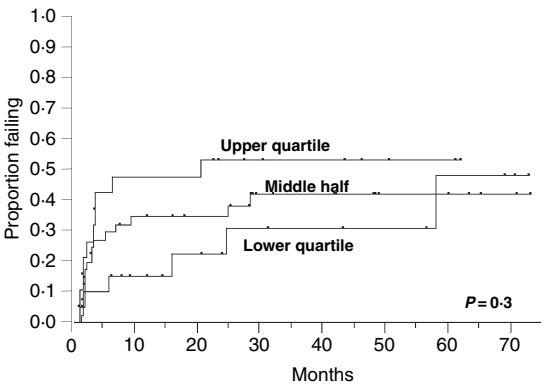

Fig 4. Cumulative incidence of relapse according to dose intensity of melphalan ($P = 0{\cdot}3$).

Effect of conditioning dose/weight on relapse and survival

Most, if not all of the therapeutic effect of autologous HSC transplantation comes from the potential of higher doses of chemotherapy to overcome mechanisms of chemo-resistance in the lymphoma cells. Therefore we hypothesized that the biological effect of the conditioning chemotherapy may correlate with dose/weight not only for toxicity but also for anti-tumor effect, leading to a comparison of CIR and overall survival among the three dose/weight groups.

Median follow up for survivors was 31·4 months at the time of this analysis. Thirty patients (37·8%) had experienced relapse of the DLBCL. CIR was not different among the three chemotherapy dose/weight groups (Fig 4; $P = 0{\cdot}3$).

Twenty-six (32·5%) patients died, three (3·9%) in absence of relapse, 21 as direct consequence of disease progression and two of other causes in patients with relapsed disease. Median overall survival for the entire cohort has not been reached. There was no difference in OS between the chemotherapy dose/weight groups ($P = 0{\cdot}8$).

Discussion

The present study found that high dose/actual weight ratio of conditioning chemotherapy predicted severe mucositis and longer hospitalization after BEAM in autologous HSC transplantation for relapsed DLBCL. However, no association was found between dose/weight ratio and relapse or survival after transplantation.

High-dose chemotherapy with autologous HSC support overcomes chemo-resistance and provides long-term disease-free survival to nearly half the patients with relapsed DLBCL with very limited transplant-related mortality (Hamlin *et al*, 2003; Buadi *et al*, 2006; Puig *et al*, 2006; Costa *et al*, 2008). BEAM remains the most commonly used conditioning regimen for autologous transplantation in DLBCL. More recently, BEAM has been combined with rituximab in a population of patients with limited prior (before salvage therapy) exposure to rituximab with apparent improvement in long-term results (Khouri *et al*, 2005). Another attempt to improve on the anti-lymphoma effect of BEAM is by its combination with anti CD 20-based radioimmunotherapy (Vose *et al*, 2005). These approaches apparently improve outcome with minimal change in toxicity and will need to be compared to BEAM in prospective studies before they can be broadly adopted.

Although death due to toxicity is a rare event in autologous transplantation for DLBCL, toxicity remains high with mucositis being its most common and challenging component. Mucositis results from interaction of patient factors (nutritional status and prior therapies) and modality of conditioning regimen and leads to marked increase in discomfort, risk of opportunistic infections (Peterson & Cariello, 2004), duration of hospitalization and cost (Sonis *et al*, 2001) associated with transplantation.

Few significant advances have been made in the prevention and treatment of mucositis in recent years. Although rhKGF (Spielberger *et al*, 2004) and rhFGF-20 hold promise, they face limitations in terms of cost, availability and lack of robust clinical data. In particular, neither of them were shown to affect the incidence or severity of mucositis with BEAM conditioning or non-TBI based conditioning for autologous transplantation, although the results of larger trials are expected.

Other authors have explored the possible association between dose/weight of chemotherapy and mucositis. Grazziutti *et al* (2006), analysed patients receiving high-dose melphalan at the University of Arkansas Myeloma program and noted that melphalan dose/kg was an independent predictor of severe mucositis. Blijlevens *et al* (2008), in an audit of 25 European transplant centres including 88 lymphoma patients, found that 42% of those undergoing BEAM conditioning developed World Health Organization (WHO) grades 3 or 4 mucositis with an association being seen between dose/weight and severity of mucositis.

Our results reinforce those ones reported by Grazziutti *et al* (2006) and Blijlevens *et al* (2008). However, there are several differences between our series and that of Blijlevens *et al* (2008). It is important to note that our study employed the NCI CTC 2.0 grading system while Blijlevens *et al* (2008) graded mucositis according to the WHO criteria, a possible explanation for the differences seen in grading (e.g. 18% of grade 4 mucositis in Blijlevens *et al* (2008) *versus* 0% in the present study). One possible limitation of Blijlevens *et al* (2008) is that patients were treated in several different institutions that probably differed in the care of transplant-associated mucositis and may have assessed mucositis heterogeneously. Our series partially overcomes such limitation because all patients were treated at the same institution, had mucositis graded prospectively by the same group of providers and during a period of time when no change was made in the institutional supportive care guidelines for management of mucositis in patients undergoing autologous transplantation.

One unique aspect of our study is that a possible correlation between conditioning dose/weight and risk of relapse and

death was explored. Although our population was homogenous in terms of disease characteristics and treatment, no effect of dose/weight ratio on risk of relapse or death could be detected.

Many different factors including the (age-adjusted) International Prognostic Index (IPI) at the time of first relapse (Moskowitz *et al*, 1999; Hamlin *et al*, 2003; Costa *et al*, 2008) and time from first line chemotherapy to first relapse (Guglielmi *et al*, 1998; Costa *et al*, 2008) have a strong influence on the risk of progression after transplantation and may potentially mask a smaller effect of chemotherapy dose/weight ratio on outcome. Another possibility is that even the lowest doses/kg reached with BSA-based dosing is enough to provide long-term disease-free survival for all patients who can be salvaged with high-dose therapy, implying no benefit for further dose intensification.

Although not statistically significant, the CIR curves obtained for each of the dose/weight groups (Fig 4) suggested that patients in the upper quartile may actually have a higher and not lower risk of relapse. This finding was corroborated by an analysis of the Center for International Blood & Marrow Transplant Research (CIBMTR) database demonstrating lower lymphoma-free survival (and higher transplant-related mortality) in underweight patients undergoing autologous transplantation for lymphoma (Navarro *et al*, 2006). One may hypothesize that, as BSA is also the parameter for dosing of first-line chemotherapy (CHOP [cyclophosphamide, doxorubicin, prednisone, vincristine]/R-CHOP [CHOP + rituximab]), patients receiving higher dose/weight of conditioning chemotherapy have indeed progressed after relatively higher doses/weight of first-line chemotherapy and have potentially more chemo-refractory disease.

Our results indicate that there may be a ''cap'' in the dose-response anti-lymphoma effect of BEAM conditioning therapy, making it appropriate to limit doses to the equivalent of 3·6 mg/kg of melphalan to prevent increased toxicity, with no detrimental impact on effectiveness. Such a strategy would require confirmation in a prospective randomized trial. Moreover there is certainly a limit of how much of the effect of chemotherapy on toxicity and efficacy can be understood by the approach employed here, because we did not factor in any pharmacokinetic or personalized pharmacogenomic information.

Lastly, our findings suggest that any further improvement in the impact of HSC transplantation in DLBCL will come from the incorporation of biological agents in the conditioning regimen rather than intensification of conventional cytotoxic agents.

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