Twenty Years of Autologous Stem Cell Transplantation in Diffuse Large B-Cell Lymphoma: A Single Portuguese Center Experience

Vinte Anos de Transplante Autólogo de Progenitores Hematopoiéticos e Linfoma Não Hodgkin Difuso de Grandes Células B: A Experiência de um Único Centro Português

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ABSTRACT

Introduction: Diffuse large B-cell lymphoma can be cured in 60% – 70% of patients. Autologous stem cell transplantation is the standard treatment for relapsed disease. This high-intensity treatment after first complete remission in patients with high International Prognostic Index remains controversial and was performed in our department during some years.

Material and Methods: Retrospective study, review of clinical records.

Results: This study evaluates the outcome of 113 patients transplanted between 1992 and 2012. Considering status before transplantation patients were divided in groups: a) first complete remission after 1 line of chemotherapy (n = 64); b) first complete remission after ≥ two chemotherapy lines (n = 15); c) second complete remission (n = 15); d) more advanced diseased (n = 19). Chemotherapy used in first line therapy was mainly R-CHOP (n = 71) and CHOP (n = 28). The median follow-up of patients still alive was 34 months (1 - 221). At five years, overall survival was 73% (± 5) and disease free survival was 75% (± 5).

Conclusion: Conventional chemotherapy followed by autologous stem cell transplant is a safe and efficient option for selected patients. In our series 70% high-risk patients were free from disease with this strategy.

Keywords: Hematopoietic Stem Cell Transplantation; Lymphoma, Large B-Cell, Diffuse; Transplantation, Autologous.

RESUMO

Introdução: O linfoma não Hodgkin difuso de grandes células B pode ser curado em 60% - 70% dos doentes. O transplante autológo de progenitores hematopoiéticos é o tratamento de intenção curativa *standard* à recidiva. Este tratamento intensivo após primeira remissão num grupo selecionado de doentes de alto risco é controverso e fez parte da estratégia do nosso Serviço durante alguns anos.

Material e Métodos: Estudo retrospectivo, consulta do processo clínico.

Resultados: Este estudo analisa o *outcome* de 113 doentes transplantados entre 1992 e 2012. Formaram-se quatro grupos com base no *status* pré-transplante: a) primeira remissão completa após 1 ciclo de quimioterapia (n = 64); b) segunda remissão completa após ≥ duas linhas de quimioterapia (n = 15); c) segunda remissão completa (n = 15); d) doença mais avançada (n = 19). O protocolo de quimioterapia de primeira linha mais utilizado foi R-CHOP (n = 71) e CHOP (n = 28). O seguimento mediano foi de 34 meses (1 - 221). Aos cinco anos a sobrevivência global foi de 73% (± 5) e a sobrevivência livre de progressão 75% (± 5).

Conclusão: A imunoquimioterapia convencional seguida de transplante autólogo é uma opção segura e eficaz no tratamento de casos selecionados de linfoma difuso de grandes células B. Na nossa casuística cerca de 70% dos doentes de alto risco atingiram remissões duráveis com esta estratégia terapêutica.

Palavras-chave: Linfoma Difuso de Grandes Células B; Transplante Autólogo; Transplante de Células-Tronco Hematopoéticas.

INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is the most common non-Hodgkin´s lymphoma accounting approximately for 40% cases in adult patients.[1-3] Despite having similar morphologic appearance, genetic and molecular research gave new insights to this disease. Currently it is known that DLBCL is not a single entity but a heterogeneous group of lymphoid malignancies. The 2008 World Health Organization classification acknowledges several subtypes of DLBCL according to the heterogeneity of molecular pathogenesis, clinical behavior and prognosis. The broader category is DLBCL not otherwise specified (NOS).[3] It is predictable that in the years to come further entities will be established, as the body of knowledge regarding the tumoral biology grows and several molecular subtypes, with distinct intracellular oncogenic pathways will be recognized.[4,5] Despite our improved understanding of DLBCL diversity the clinical practice remains remarkably uniform. Regarding prognosis several prognostic models and biomarkers were investigated but lack validation.[6-9] While one can speculate that improved prognostication will be crucial to allow individualized risk-adapted therapy in the future, at the present time the International Prognostic Index (IPI), based on clinical

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parameters, remains the single validated prognostic tool used in clinical routine. However it is recognized that these clinical parameters reflect a mixture of underlying biologic or genetic differences and have limitations to identify a very poor risk group of patients. Also, the prognostic of patients who have identical IPI values can vary considerably.[6-11]

On the other hand a molecular tailored treatment approach is still far from clinical routine practice, despite several clinical trials are investigating this.[12-15] Currently, the standard treatment approach is combination chemotherapy and the monoclonal antibody rituximab.[16-21] The introduction of immunochemotherapy as frontline treatment has significantly increased complete remission rate and survival. Depending on age at diagnosis and other prognostic factors, up to 70% patients can achieve a complete remission (CR).[21]

Despite the high CR rate, the outcome of patients with intermediate or high IPI is still dismal. For these patients the better treatment strategy is uncertain and there is a need for randomized prospective clinical trials in the rituximab era.[21] Several different approaches deviating from standard R-CHOP were proposed in the literature: shorten the interval of administration of chemotherapy drugs (R-CHOP 14) or protocols based on higher dose-intensity (R-ACVBP, R-CHOEP). Also, in the view of the established benefit of autologous stem cell transplant (Auto-SCT) in salvage setting, this strategy has been explored as upfront therapy in poor-risk patients.[22-32] Based on this studies our department offered systematically Auto-SCT as first line consolidation treatment in young patients with IPI ≥ 2 during the period considered in this review. All these strategies raise concerns of acute and delayed toxicity. So far, better therapeutic alternatives to R-CHOP, without substantial additional toxicity, have not been found.

In the setting of relapsed or refractory disease, the prognosis is poor. A salvage regimen followed in responsive patients by high dose treatment with stem cell support is recommended with curative intent.[20,32-36]

The aim of this study was to review twenty years of one single center experience with Auto-SCT in DLBCL. It reflects the clinical routine reality and contributes to a better understanding of the outcome of these patients. Also, the role of Auto-SCT as a frontline therapy remains to be defined and the authors hope to contribute to the body of experience with transplantation in this setting (review of 64 high risk patients transplanted in first CR).

MATERIALS AND METHODS

This study was a retrospective single center analysis including all consecutive Auto-SCT performed in adult patients with DLBCL, between October 1992 and December 2012. Data were collected from the service database and medical records. Statistical analysis was performed with SPSS v21. Event-free and overall survival was analyzed by the log-rank test and the results were expressed as Kaplan–Meier plots. A univariate analysis was performed to assess prognostic factors before Auto-SCT. A multivariate analysis was performed to evaluate the impact of the different prognosis variables.

During the considered period 152 Auto-SCT were performed in various histological subtypes of DLBCL. We included in the statistical analysis 113 patients with DLBCL not otherwise specified and excluded all the histological variants (primary mediastinal large B-cell lymphoma and histological transformation of 'low grade' lymphomas). Considering the IPI at diagnosis in the patients in 1st complete remission and disease status at transplantation, the patients were divided in four groups: 1) patients in first complete remission after first line chemotherapy and with IPI > 1; 2) patients in first complete remission after two or more lines of chemotherapy; 3) patients in second complete remission; 4) patients not fitting in the other groups.

RESULTS

The median age at the time of Auto-SCT was 49 years (16 - 67). The majority of patients were males (n = 68). The majority of patients presented advanced stage (85%) and IPI 2 or 3 (47% and 30% respectively) at diagnosis (Table 1).

The distribution of the patients according to the four groups considered and IPI at diagnosis is shown in Table 2 Rituximab was used in 78 patients before Auto-SCT (66%). The most frequently used first line chemotherapy was R-CHOP (n = 71) and CHOP (n = 28). High dose chemotherapy consisted of standard BEAM regimen (n = 93) or FEAM (n = 20). Hematopoietic stem cells were collected from peripheral blood (PBSC) (n = 100), bone marrow (BM) (n = 2), and PBSC + BM (n = 11). Sixty seven transplants (59%) were performed in the last five years of the period. The median follow up of patients still alive was 34 months (1 - 221). The overall survival (OS) at one, three and five years was 84.6% (± 3.4); 75,1%(± 4.4); 73%(± 4.8) respectively. (Fig. 1). Significant differences in OS were found among the 4 groups considered (p = 0.001) (Table 3).

The OS of the group one was not significantly different from the group two or three; the difference to the group four was significant ($p < 0.001$); the OS was also significant between group two and four ($p = 0.014$); this difference was not significant between group two and three ($p = 0.4$) or group three and four ($p = 0.067$).

The disease free survival (DFS) at one, three and five years was 84% (± 4); 80% (± 4); 75% (± 5), respectively.

Table 1 – Overall patients characteristics

Patients characteristics	n (%)
Total	113
Age at Auto-SCT	49 [16 - 67]
Male/Female	68/45
Stage Ann Arbor	
I/II	16 (14%)
III/IV	97 (86%)

Table 2 – Distribution of patients in four groups based on International Prognostic Index at diagnosis and disease status at Auto-SCT.

	Group 1	Group 2	Group 3	Group 4
Status before transplantation	1st CR after 1 chemotherapy line	1st CR after ≥ 2 chemotherapy lines	2nd CR	more advanced disease
n	64	15	15	19
IPI 0/1	0	2	7	4
IPI 2	33	10	4	6
IPI 3	24	3	2	5
IPI 4	6	0	2	4
IPI 5	1	0	0	0

CR: complete remission

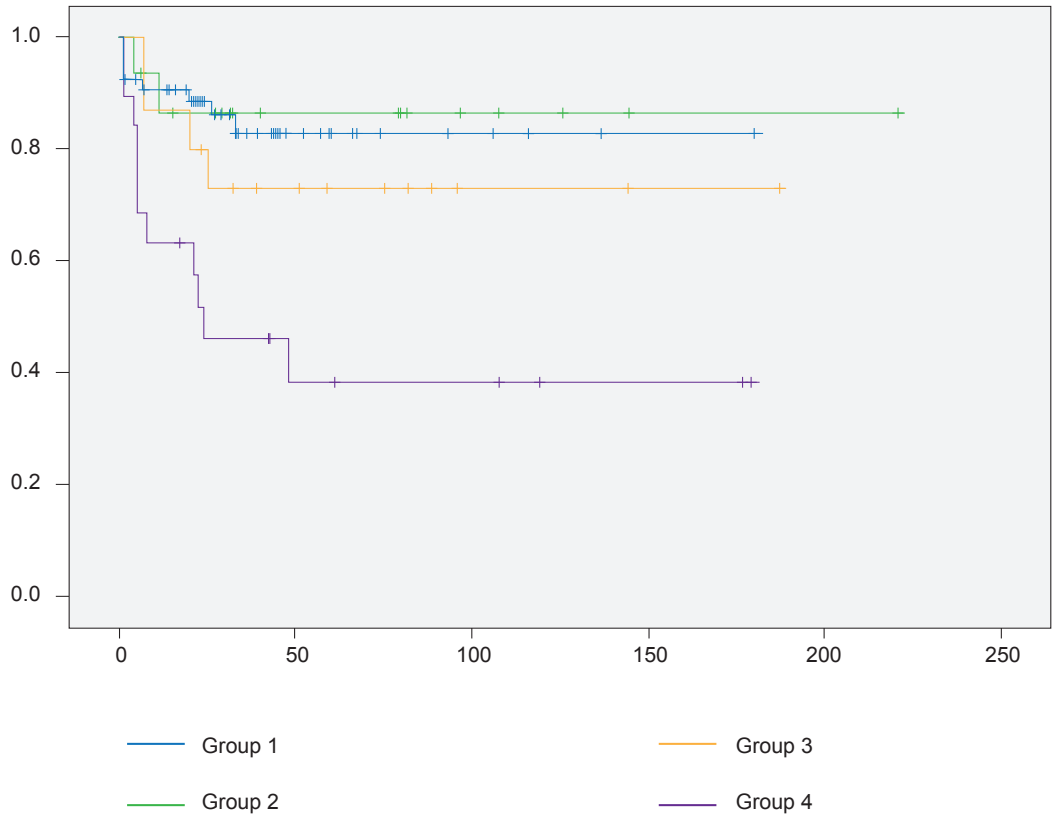

Figure 1 - Kaplan-Meyer estimates of overall survival, based on the four groups of patients

Table 3 – Overall survival and non-relapse mortality among the four groups of patients based on International Prognostic Index at diagnosis and disease status at Auto-SCT

	Global population	Group 1	Group 2	Group 3	Group 4
OS 1 year	84.6 (3.4)	90.5 (3.7)	86.2 (9.1)	72.7 (11.7)	63.2 (11.1)
OS 3 years	75.1 (4.4)	82.7 (5.5)	86.2 (9.1)	72.7 (11.7)	45.9 (11.7)
OS 5 years	73.0 (4.8)	82.7 (5.5)	86.2 (9.1)	72.7 (11.7)	38.2 (12.0)
OS 10 years	73.0 (4.8)	-	-	-	-
Non-relapse mortality 1 year		7.8 + 3.4%	0	6.7 + 6.4%	10.5 + 7%

Causes of death were: relapse/progression (n = 17); non-relapsed mortality (n = 8); and secondary neoplasia (n = 1, myelodysplastic syndrome) – Table 3.

In univariate analysis, OS was significantly longer if: early stage at diagnosis, less than two chemotherapy lines before Auto-SCT, disease status before Auto-SCT in CR, first line chemotherapy with RCHOP and use of PBSC. However, when performing multivariate analysis the differences became non-significant.

DISCUSSION

The aim of this study was to review one single center experience with Auto-SCT in DLBCL. Our results clearly demonstrate that the outcome of patients treated with Auto-SCT is dependent on disease status before transplantation, consistent with the published literature.[31] Failure to achieve CR with first line standard immunochemotherapy is considered poor prognostic characteristic. However in our series it did not have a relevant impact in the outcome if the patient achieved CR with second line chemotherapy (Group two). Even though in the univariate analysis we found a better outcome in patients that had received rituximab (p = 0.009), our data does not allow precise measurements specially because the broad temporal span of this series.

While it is well known that patients with IPI ≥ 2 at diagnosis have a worse outcome there is a lack of knowledge regarding the best treatment option in this setting.[8] Auto-SCT as first line consolidation treatment is an option in young patients but the value of upfront Auto-SCT is yet to be determined and remains experimental.[25-31] Recently SWOG-intergroup 9 704 trial failed to show improved OS, though EFS was seen.[32] Our data shows that this group of patients (Group one) experienced good OS with this treatment strategy. Toxicity is a concern and there is no solid data comparing prospectively upfront Auto-SCT consolidation versus first line treatment with high dose/intensive chemotherapy protocols alternative to standard R-CHOP. In our population non-relapsed mortality was in the expected range, consistent with the published literature. The morbidity and mortality of Auto-SCT must be considered when this treatment is proposed.

At relapse salvage chemotherapy followed by Auto-SCT is the standard second line treatment. This strategy can rescue many patients if the disease remains chemosensitive.[20,33-36] In our series, as expected, patients with refractory disease had a dismal prognosis, even with high-dose therapy.

CONCLUSION

In spite of the improved outcome in the rituximab era, many patients with DLBCL still have poor prognosis. Our study shows that Auto-SCT is a good therapy option for high-risk disease, with acceptable non-relapse mortality. About 70% of high risk patients were free of disease after conventional chemotherapy followed by Auto-SCT. While being the standard treatment option in the setting of relapsed disease, much controversy remains about the role of Auto-SCT as an upfront treatment option. Also, since most studies addressing Auto-SCT were performed in the pre-rituximab era, there is a need to redefine the role of this treatment strategy nowadays. There is a need to perform randomized trials to determine if Auto-SCT improves the outcome in high-risk patients treated with rituximab based chemotherapy. On the other hand, further knowledge of additional prognosis factors is necessary. Hopefully the incorporation on clinical practice of novel validated biomarkers and functional imaging techniques such as PET scan will in the future help to further stratify young patients with poor risk classical prognosis factors, contributing to select the ones most prone to benefit with upfront Auto-SCT.[8-11]

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patient's data publication.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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