

Review / Revisão

The issue of refractory disease in follicular and other lymphoma subtypes

A refratariedade no linfoma folicular e em outros linfomas

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The outcome of lymphoma has definitely improved over the last few decades which is mainly due to the introduction and development of novel and effective therapeutic approaches. Nevertheless, a small though notable group of patients may display a poor response to treatments, with a true refractoriness or a transient response followed by early relapse. The present review addresses the issue of refractory disease among patients with lymphoma, focusing on the overall incidence and the main clinical aspects associated with refractoriness. *Rev. Bras. Hematol. Hemoter.* 2009;**31**(Supl. 2):15-18.

Key words: Hodgkin's lymphoma; non-Hodgkin's lymphoma; chemotherapy; autologous stem cell transplantation; refractory disease.

Introduction

Hodgkin's (HL) and non-Hodgkin's (NHL) lymphomas are malignant tumors usually characterized by a high response-rate to chemo-radiotherapy. Among NHL, peculiar epidemiology features have been observed, with the incidence progressively increasing over the last 50 years up to the value of 19.5 per 100,000 individuals per year, based on cases diagnosed in 2002-2006. Indeed, the incidence of NHL has increased 0.6% per year during the period 1991-2004, while mortality clearly shows a decrease of 3.2% per year. For HL, the incidence has been decreasing slightly over the last 30 years, dropping to the value of 2.8 per 100,000 individuals per year (2002-2006 diagnoses). Again, the mortality rate of HL has shown a marked reduction, with trend rates analogous to those observed in NHL. At present, the overall age-adjusted mortality rate of NHL is 7.1 per 100,000/year and 0.4 per 100,000/year for HL according to the most recent survey by

SEER.¹ Thus, the outcome of lymphoma has definitely improved over the last few decades which is mainly due to the introduction and development of novel and effective therapeutic approaches.

In the field of lymphoma, several treatment options have been successfully employed, including high dose chemotherapy, autologous stem cell transplantation and different classes of new biological drugs, in particular the chimerical and humanized monoclonal antibodies directed against lymphocyte-specific antigens. Progressively, a great fraction of patients can now obtain complete response, which is often durable. This results in prolonged survival which frequently means the cure of an otherwise fatal malignant disease. Nevertheless, a small though notable group of patients may display a poor response to treatment, with true refractoriness or a transient response followed by early relapse. Appropriate studies are needed to identify possible early predictors of refractory disease. This will allow the

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investigation of novel therapeutic programs suitable for patients at high risk of poor response to standard treatment approaches.

The present review addresses the issue of refractory disease among patients with lymphoma, focusing on the overall incidence and the main clinical aspects associated with refractoriness.

Refractory disease in high-risk follicular lymphoma

To evaluate the efficacy of high-dose therapy and ASCT in the treatment of Follicular Lymphoma (FL) a randomized multicenter trial comparing intensive therapy vs. conventional chemotherapy, both supplemented with Rituximab, has recently been performed in high-risk FL at diagnosis. Most Italian Centers associated to GITMO (Gruppo Italiano Trapianto Midollo Osseo) and to IIL (Intergruppo Italiano Linfomi) participated to the study. The intensive arm was the high-dose sequential (HDS) schedule, developed several years ago for FL and other indolent lymphoma² while the conventional arm was the well known CHOP (cyclophosphamide/doxorubicin/vincristine/prednisone) scheme. Four to six doses were included in the HDS scheme (R-HDS) and at completion of 6 CHOP courses (CHOP-R). Overall, 136 patients were enrolled and evaluable for response to treatment. Preliminary results have been recently reported in Blood.³ In summary, R-HDS proved to have a more potent anti-lymphoma activity compared to CHOP-R, with 4-year EFS of 61% and 28%, respectively (P < .001), at a median follow-up (MFU) of 51 months. However, this did not translate in survival advantages. Indeed, no difference in overall survival (OS) was observed between patients of the two treatment arms. Interestingly, molecular remission (MR) was achieved in 44% of CHOP-R and 80% of R-HDS patients (P < .001), and was the strongest independent outcome predictor.

The presence of refractory patients was clearly documented in this randomized study. As shown in Table 1, complete remission (CR) was 62% with CHOP-R and 85%

Table 1. Response according to treatment arm of 136 high risk FL patients enrolled in the GITMO/IIL randomized study

Parameters of response	CHOP-R	R-HDS	p
CR/Cru	62%	85%	< .001
PR	7%	3%	NS
OR (CR+PR)	68%	89%	<.01
Progression or stable disease	29%	10%	<.05
Not Evaluable	3%	2%	NS
Total n° of patients	68 (100%)	68 (100%)	

CR= Complete Remission; Cru=CR undefined; PR= partial remission; OR=overall response, according to Cheson's criteria of response²²

Table 2. Efficacy of R-HDS in the rescue of FL patients progressing after CHOP-R

Rescue Program	Total	CR	
Minimal treatment *	11	6	54%
Conventional CT **	8	6	75%
R-HDS	24	30	80%
Allogeneic Transplantation	1	1	100%

* Rituximab +/- Radiotherapy; **Fludarabine containing chemotherapy; R-HDS= High Dose Sequential scheme

with R-HDS (P < .001). The difference in the rate of CR was mainly due to the different proportion of non-responding, i.e. refractory, patients. In fact, approximately 30% of patients receiving CHOP-R had a poor response, displaying progressive or stable disease; poor responders were approximately 10% in the R-HDS arm. Thus, in spite of the effective treatment delivered (CHOP or HDS both supplemented with rituximab) there is still a variable, non-negligible, group of patients displaying refractory disease. The cross-over design of the study offered a good opportunity of rescue to patients failing after CHOP-R. Indeed, patients refractory or early-relapsing after CHOP-R underwent salvage with R-HDS. As shown in Table 2, salvage R-HDS had an 80% CR rate and a 68% 3-year EFS (MFU, 30 months). Thus, most patients with poor response to CHOP-R experienced a prolonged survival following R-HDS as rescue and this explains the lack of difference in OS between the two treatment arms. In conclusion, the study offered several important insights for the management of high-risk FL. In particular, it has been confirmed that achieving CR and MR is critical for effective disease control, regardless of which treatment is used; overall, R-HDS given front-line ensures superior disease control and molecular outcome than CHOP-R, but no improvement in OS; lastly, the presence of FL patients with refractory disease is a major concern, particularly with conventional chemo-immunotherapy such as CHOP-R; however, primary failures after CHOP-R have a good outcome if rescued with R-HDS. Taken together, all these aspects suggest that relapsed/refractory FL might be the most appropriate setting for R-HDS-like treatments.

Incidence of refractory disease in NHL other than follicular subtype

To increase cure rates in patients with aggressive or refractory/relapsing NHL, intensive treatments and ASCT have been extensively investigated, mostly in patients younger than 60 to 65 years.^{4,5} Applicability and efficacy of the HDS approach has been improved by the use of mobilized peripheral blood cells (PBSC) for the autograft procedure.^{6,7} Moreover, the use of agents such as the monoclonal anti-CD20 antibody and rituximab (R), has markedly improved the therapeutic efficacy of ASCT-based programs by the in vivo

purging effect on PBSC harvests, as reported by other groups and by a recent study from our cooperative GITIL (Gruppo Italiano Terapie Innovative nei Linfomi) group.⁸⁻¹²

In the setting of Diffuse Large B-cell lymphoma (DLB-CL), the GITIL group has recently completed a prospective multicenter study evaluating the rituximab-supplemented, early-intensified high-dose chemotherapy regimen, delivered with multiple autologous support using in-vivo purged PBPC, in a series of 112 previously untreated patients with DLB-CL and aaIPI 2 or 3. Both response and long-term outcome were definitely promising, and compare quite favorably with the dismal outcome commonly observed in poor-risk DLB-CL treated with conventional chemotherapy regimens.¹³ Overall 90 patients (80.4%) reached CR. However, again the major cause of treatment failure was disease progression, documented in 12 (11%) patients. This is consistent with the selection of a true poor-risk patient population, with some cases displaying a highly refractory disease, unresponsive to repeated courses of high-dose cytotoxic drugs given at short intervals. Moreover, the result confirms that a variable proportion of NHL patients may be primary refractory, even to high-dose therapy with rituximab.

In order to assess the real number of NHL patients with refractory or early-relapsing disease, a recent study was undertaken to evaluate the actual rate of refractory patients. The long-term outcome of primary refractory vs. responsive patients is also under evaluation. Data have been collected on a series of 503 NHL patients referred and treated at our institutions between 1995 and 2005. The group included 461 B-cell and 42 T-cell NHL; main histological subtypes consisted of: 305 high-grade NHL, 183 low-grade NHL and 15 mantle-cell lymphoma. Overall, 126 (25%) patients were refractory (39% with no response at all and 61% with short-lasting response soon followed by disease progression). The rate of refractoriness was as high as 40% in the small T-cell NHL subgroup, while the overall incidence was 24% for B-cell NHL. There was no significant difference in the distribution of refractory patients among the histological subtypes of B-NHL, in other words none of the B-cell NHL subtypes was specifically associated with poorer response to treatment. The use of the HDS program as front-line treatment was significantly associated with reduced risk of refractory disease (OR=0.30). These data apparently suggest that better outcome could derive by an early use of the HDS approach in newly diagnosed NHL with advanced stage of disease and other typical clinical features of poor prognosis.¹⁴ Indeed, further studies are still needed, in order to identify patients unfit to receive conventional treatment due to poorly responsive disease as early as possible. For these patients, the prompt institution of alternative treatment approaches might increase the chances of achieving disease remission.

At present, therapeutic procedures available for the rescue of patients displaying overt refractory disease apparently do not improve the chance of long-term survival.

Life expectancy remains dramatically poor for patients with refractory or early relapsing disease. Indeed, in our analysis it was possible to observe that refractory patients had a definitely short life expectancy, with a median survival of 21 months and a 14-year survival projection of 10%, which is markedly worse compared to the 88%, 76% and 65% survival projections at 5, 10 and 15 years, respectively, of responsive patients. Several studies have shown some efficacy of ASCT in the salvage treatment of NHL.^{4, 5, 15} In addition, allogeneic stem cell transplantation is an effective treatment option which seems to improve the outcome of refractory patients, particularly since the development of the reduced intensity conditioning regimen (RIC).¹⁶

Conclusion

The results herein presented indicate that a non-negligible proportion of NHL patients have refractory disease. Overall, refractory patients represent approximately one quarter of NHL cases undergoing induction therapy. Besides advanced stage and high LDH levels, no other clinical and histological factors are specifically associated to refractoriness; indeed, further studies are needed to identify possible molecular markers predictive of refractoriness in order to design induction therapies adapted for refractory patients given their dismal outcome with currently available treatment strategies. A lot of new small molecules that target bcl-2, bcl-6, mTOR, the AKT pathway (deforolimus), P-glycoprotein (Zosuquidar), histone deacetylase (SAHA) and NF-kB have shown promising activity in preclinical and early-phase clinical studies.^{17,18} Moreover, a clear benefit has been documented with some new drugs or combination of drugs, including lenalidomide, bendamustine and the radiolabeled anti-CD20 Zevalin.^{19,20,21} New targets and new drugs should be carefully considered as an important tool in the effort to improve the very poor outcome of patients with refractory lymphoma.

Resumo

A evolução dos linfomas tem sido definitivamente melhorada ao longo das últimas décadas. Isto se deve principalmente devido à introdução e desenvolvimento de novas e efetivas abordagens terapêuticas. Apesar disto, uma pequena parcela deste notável grupo de pacientes pode apresentar uma pobre resposta aos tratamentos, com uma verdadeira refratariedade, ou com resposta transitória e precocemente uma recidiva. A presente revisão aborda este assunto da doença refratária nos pacientes com linfoma, enfocando sua incidência global e os principais aspectos clínicos associados à refratariedade. Rev. Bras. Hematol. Hemoter. 2009; 31(Supl. 2):15-18.

Palavras-chave: Linfoma de Hodgkin; linfomas não Hodgkin; quimioterapia; transplante autólogo de células-tronco; doença refratária.

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