

## Artigo Especial / Special Article

**Autologous stem cell transplantation for aggressive non-Hodgkin's lymphomas**

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*Autologous stem cell transplantation (ASCT) has been seen to overcome resistance, allowing an increase in the dose of available drugs and radiotherapy. Initially used after first-line for relapsed or refractory non-Hodgkin's lymphomas (NHL), ASCT has since been used in more favourable clinical conditions such as partial remission (PR), first complete remission, and as front-line therapy following chemotherapy. High-dose chemotherapy and autologous stem-cell transplantation has now become the standard care for eligible patients with recurrent, chemosensitive aggressive NHL. Primary refractory patients and resistant relapse are not good indications and should be considered a group eligible for phase II studies.*

*There may also be a role in patients with partially responsive disease. However new and larger randomised studies are needed to clarify this question.*

*A challenge for lymphoma management is the evaluation of the role of high-dose therapy and ASCT as an initial treatment in aggressive NHL, identifying patients who will not be cured with standard therapy. A series of concurrent or retrospective analysis would indicate so-called "higher-risk patients", as defined by the IPI, as potential targets for intensified therapy. However, according to published data, the problem remains open to debate. Larger, randomised studies are necessary and welcome and this should be considered a high priority.*

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**Introduction**

Over the last ten years, claims have been made that second and third generation chemotherapy (CT) regimens have improved survival in the advanced stage, intermediate or high-grade malignancy non-Hodgkin's lymphomas (NHL) (Groups F-G-H-K/Working Formulation, excluding lymphoblastic and Burkitt lymphoma)<sup>1</sup>. In spite of this, the percentage of achievable

complete remission (CR) is between 50% to 70%, and about 50% of these patients later relapse<sup>2,4</sup>. Consequently, the probability of long-term real cure is about 35%.

Negative prognostic factors, together with histologic subtypes and advanced stage, affect on the one hand, both the possibility of obtaining CR and survival, and on the other, CR maintenance and disease-free survival (DFS) (5).

Failure to obtain CR, or subsequent relapse,

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had serious consequences on the course of these lymphomas, because second-line therapies offer poor possibility of salvage (6-8).

Autologous stem cell transplantation (ASCT) has been seen to overcome resistance, allowing an increase in the dose of available drugs and radiotherapy. Stem cell rescue can shorten the hypoplastic period decreasing life-threatening risks. Initially used after first-line for relapsed or refractory NHL, ASCT has since been used in more favourable clinical conditions such as partial remission (PR), first CR, and as front-line therapy following CT.

## ASCT as salvage treatment in relapsed or refractory NHL

The conventional management of refractory or relapsing NHL is usually associated with poor results. About 30% of patients achieve CR, but median survival time is less than 1 year, 3-year probability of survival is from less than 20% to 30%, and 3-year probability of time to treatment failure is less than 10% (6-8).

The first historical 152 patients, observed after joining together small groups of relapsed or refractory patients treated with ASCT by various authors (unpublished data from: Appelbaum, Armitage, Philip, Phillips, Ricci, Santini, Verdonck), showed these patients were able to achieve a CR rate of 59%. About 50% of patients later relapsed. In conclusion about 25% of patients maintained CR status. However, an initial stratification of these patients in two groups, true chemoresistant on the one hand, and chemosensitive on the other (sensitive relapse and PR), showed that probability to achieve and maintain CR was very poor (less than 10%) in chemoresistant patients. This initial observation was well defined by Philip et al. (1987) (9), who pointed out three groups of patients with different outcomes after ASCT. Sensitive relapse patients, after CR, had a 3-year DFS probability of 36%, while resistant relapse and refractory patients had a DFS of 14% and of 0%, respectively. The problem of truly resistant patients (resistant relapse and refractory patients)<sup>10</sup> remains unresolved. Our personal experience<sup>10</sup> in this subset of patients, using high-dose

cyclophosphamide (7 gr/sm) followed by BEAM regimen and ASCT shows a 5-year progression-free survival probability of 11%.

The Parma randomised trial, published by Philip et al. in 1995 (11), clarifies the role of ASCT in relapsed patients. Two hundred and fifteen patients in relapse, with aggressive NHL, were treated with DHAP chemotherapy for two courses. One hundred and nine chemosensitive patients were randomly assigned to receive DHAP for 4 courses plus radiotherapy *versus* BEAC regimen and ASCT. The response rate was 83.7% in ASCT arm and 42.5% in conventional CT arm. Five-year probability of survival was 53% *versus* 32% in the two arms ( $p=0.03$ ) respectively, in favour of the intensified therapy arm. Similar results were observed in terms of event-free survival: 46% in ASCT arm, and 12% in conventional arm ( $p=0.001$ ), respectively.

Following these results, ASCT has been considered the standard treatment of aggressive NHL in sensitive relapse.

## ASCT as the primary treatment for aggressive non-Hodgkin's lymphoma

### 1) In partial remission

Survival of patients responding to initial chemotherapy but not in remission after induction is very poor, in spite of salvage treatment. The median survival duration ranges from between 5 and 14 months, with a 2-year survival probability of less than 30% (6-8, 12).

Following the concept that ASCT can cure about 50% of chemosensitive relapsed patients, ASCT procedure was applied in a subset of patients who partially responded to front-line therapy. In 1988 Philip et al. (13) reported interesting results in 17 patients treated with high-dose therapy and ASCT while in PR after conventional CT. Thirteen patients (76%) are disease-free, with a 6-year survival probability of 75% after ASCT. In 1993 the Non-Hodgkin's Lymphoma Co-operative Study showed an overall probability of DFS of 36% at 5 years in 21 patients, suggesting a potential cure of about one in three patients autotransplanted in PR after front-line therapy (14).

Only two randomised studies have been

published in this field. In 1995, Verdonck et al. (15) evaluated the impact of ASCT in patients who failed to achieved CR after 3 courses of CHOP therapy. Patients were randomised to receive high-dose therapy plus ASCT or 5 additional courses of CHOP chemotherapy. The majority of patients enrolled in this trial had low and low to intermediate risk disease (5). The study failed to demonstrate any benefit from ASCT in first PR patients. On the contrary, a trend in favour of conventional therapy was reported.

In 1996, Martelli et al. (16) reported results of a randomised study designed to evaluate, by a second randomisation, the effect of DHAP *versus* ASCT in aggressive NHL in early PR after first-line therapy. A group of 286 patients entered first randomisation and 49 second randomisation. Twenty-seven patients entered the DHAP arm and 22 the ASCT arm. CR was achieved in 59% of DHAP patients and in 96% of ASCT patients, respectively. The probability of progression-free survival (PFS) was 73% for ASCT and 52% for DHAP, with a probability of survival of 73% and 59%, respectively. However, because of the small number of patients involved, the study was unable to determine whether ASCT or a standard salvage therapy is better for PR patients.

We must conclude that the problem of ASCT in PR patients remains unresolved.

## 2) In 1<sup>st</sup> complete remission

Following the failure of 2<sup>nd</sup> and 3<sup>rd</sup> generation regimens over 1<sup>st</sup> generation in improving outcome in aggressive advanced stage NHL, a series of studies were carried out in favourable situations on patients in CR after front-line therapy. In these CR patients we expect a relapse rate ranging from 40 to 50%, in spite of received treatment (2-4).

In 1994, following single phase II studies suggesting a potential benefit of ASCT for 1<sup>st</sup> CR aggressive NHL (17, 18), the French Group published a randomised study in which entered 790 patients with aggressive NHL who had at least one adverse prognostic factor (19). Following an initial randomisation on anthracycline, 464 patients in 1<sup>st</sup> CR after induction therapy were randomised to receive high-dose therapy (CVB) plus ASCT or a consolidative sequential therapy including

ifosfamide, etoposide, asparaginase, and cytarabine. With a median follow-up duration of 28 months, the 3-year DFS was similar in both arms, 52% in the sequential arm and 59% in the ASCT arm ( $p=0.46$ ). Overall survival was once again similar, at 71% and 69% respectively ( $p=0.60$ ). A retrospective analysis showed a positive trend in favour of higher-risk patients (2-3 negative factors at diagnosis), as defined by the I.P.I. adjusted for age < 60 years (5), who had received ASCT. Successive, intermediate and final analyses published by the same Group in 1997 and in 2000 confirm a statistical benefit of ASCT over sequential therapy in higher-risk NHL in terms of DFS (59% and 39% at 5 years, respectively,  $p=0.01$ ) (20), and in terms of overall survival (64% and 49% at 8 years, respectively,  $p=0.04$ ) (21).

The hypothesis that ASCT could improve outcome in higher-risk patients has also been reported by Pettengell et al. (22) in 1996 and by Santini for the NHLCSG (23) in 1998. The first author found a statistically better outcome in terms of survival and PFS in favour of patients receiving ASCT, but the study includes two successive, not randomised, cohorts of patients. The second study showed a statistical improvement for patients treated with ASCT in terms of DFS, but this was only a retrospective analysis, and the study does not include higher-risk patients randomised at diagnosis.

In 2001 a randomised study proposed by Vitolo et al (24) does not confirm any difference in response rate and outcome of higher-risk patients treated with high-dose sequential therapy (HDS: APO, high-dose/cyclophosphamide, high-dose methotrexate, high-dose VP16) plus high-dose therapy and ASCT *versus* patients treated with an intensified outpatient CT. A second retrospective analysis of a randomised study presented in 2002 by Santini for the NHLCSG (25) does not show any difference in terms of survival and PFS for patients treated with VACOP-B + high-dose sequential therapy (high-dose/cytoxan, high-dose VP16), BEAM regimen and ASCT *versus* patients treated with VACOP-B (plus HDS and ASCT in case of persistent disease after front-line therapy).

A more recent study published in 2002 by

Gisselbrecht et al (26) compared an experimental shortened treatment followed by high-dose therapy and ASCT *versus* ACVBP regimen plus sequential consolidation therapy in 370 higher-risk patients younger than 60 years. Results showed a statistical better survival and event-free survival in favour of patients treated with ACVBP conventional treatment. The conclusive comment was that the received dose-intensity before high-dose therapy was too low and that ASCT was given too early.

In conclusion, the real benefit of ASCT over conventional therapy for higher-risk patients is still open to debate.

### 3) After full-course standard induction therapy

The results observed with ASCT in other clinical situations have led many investigators to extend this aggressive approach as part of the initial therapy in aggressive advanced stage NHL.

In 1997, Vitolo et al. (27) reported a phase II study in which 50 high-risk patients, presenting advanced stage disease at diagnosis with high tumour burden and elevated lactate dehydrogenase level or bone marrow involvement, were treated with an escalating sequential therapy. Patients received MACOP-B for 8 weeks followed by intensified therapy (mitoxantrone, high-dose ARA-C, dexamethasone), BEAM regimen and ASCT. This study showed a progressive increased response rate according to the number of chemotherapy steps with a final CR rate of 72%. With a median follow-up time of 32 months from the start of treatment, overall survival and failure-free survival rates are 56% and 50%, respectively. In conclusion, the sequential scheme with intensified and high-dose CT with ASCT was seen to be feasible, with an improved outcome in a poor category of patients.

In 2000, the NHLCSG (28) reported similar results in 40 patients with bone marrow involvement at diagnosis. Patients received VACOP-B for 8 weeks, high-dose cyclophosphamide ( $7 \text{ gr/m}^2$ ), BEAM regimen and ASCT. CR rate improved according to the various steps and, at the completion of treatment was 72.5%. The actuarial 3-year overall survival, DFS and failure-free survival were 48%, 55% and 40%, respectively.

Randomised studies are currently in progress, and in 1997 Gianni et al (29) reported on 98 patients with diffuse high-risk, large B-cell NHL (Groups G and H/WF), who were randomised to either standard therapy with MACOP-B, or HDS (six chemotherapeutic agents administered sequentially at a high dose) followed by high-dose therapy and ASCT. In this study, T-cell lymphoma and patients with bone marrow involvement were excluded. After a median follow-up of 55 months, patients treated with HDS had a significantly better outcome when compared with those receiving MACOP-B. CR rate was 96% *vs* 49% ( $p=0.001$ ), freedom from progression 84% *vs* 49% ( $p<0.001$ ), freedom from relapse 88% *vs* 70% ( $p=0.055$ ), and event-free survival 76% *vs* 49% ( $p=0.004$ ) in the two arms respectively. Overall survival, in spite of a large trend in favour of HDS, showed no statistical difference (81% *vs* 55%,  $p=0.09$ ). The conclusion was that HDS is superior to standard therapy for patients with diffuse large B-cell NHL.

In 1998, Santini for the NHLCSG (23) published results on 124 patients with diffuse, mixed and large-cell type NHL, randomised at study entry to receive standard induction VACOP-B therapy alone or the same regimen followed by ASCT. Patients had less than 60 years of age with stage II bulky (tumour > 10 cm) or stage III-IV disease. Patients with initial bone marrow involvement were excluded. Patients who were randomised to receive standard induction therapy and achieved a CR simply went to follow-up. Patients with persistent disease after induction or who relapsed underwent DHAP salvage regimen. Patients randomised to receive VACOP-B and ASCT, in CR, PR, or non-responders to induction therapy proceeded to ASCT. Complete remission was similar in the two arms (75% and 73%, respectively). With a median follow-up observation of 42 months, 6-year survival probability was 65% in both arms. There was no difference in DFS or PFS between the two groups of patients. However, as reported before, when outcome was analysed on the basis of age-adjusted IPI at diagnosis, patients with high-intermediate or high-risk disease were more likely

to remain disease-free if they received additional ASCT (3-year DFS rate, 87% for ASCT vs 48% for standard therapy,  $p=0.008$ ). In conclusion, this study showed an apparent improvement in survival (65% in both arms) compared with the survival of about 50% to be expected with a conventional front-line therapy.

Following all these considerations, in 2002 the NHLCSG (25) reported interim results of a new study in which patients with aggressive, advanced stage NHL were randomised to receive VACOP-B (+ HDS in case of persistent disease) vs VACOP-B + HDS (CY, 7 gr/m<sup>2</sup>; VP 16, 2 gr/m<sup>2</sup> and BEAM + PBPC rescue) in all cases. The aims of the study were: a) to confirm the Milan Group's data; and b) to evaluate the possible use of HDS only when necessary. Two-hundred and twenty-three patients with mixed and large-cell NHL (Groups F/G/H/K-WF) aged from 15 to 59 years, in stage II bulky > 10 cm, III and IV were included. All categories of patients, with B- and T-cell phenotype, and with initial bone marrow involvement were entered. When results were analysed, 223 patients were evaluable for response. A third interim analysis shows CR of 65% and 67% respectively. With a median observation time of 37 months, actuarial curves show a 6-yr probability of survival and of PFS of 51% and 47% respectively, with no difference between the two arms.

When only B-cell type, G and H/WF NHL without BM involvement were analysed, probability of survival improved to 70% (conventional arm) and 80% (intensified arm), and PFS to 50% and 64%, respectively. Patients with T-cell type NHL and with BM involvement showed the poorest results. When patients with BM involvement were excluded, the probability of survival and PFS were 57% and 66%, and 48% and 54% in the two arms respectively. When outcome was analysed according to age-adjusted IPI at diagnosis, lower-risk patients (0-1 negative factors at diagnosis) showed a better statistical outcome compared with those at higher-risk (2-3 negative factors at diagnosis). Survival was 74% vs 46% ( $p=0.0001$ ) and PFS 57% vs 40% ( $p=0.0001$ ), respectively. When these two groups were analysed no difference was seen between them.

This analysis seems to confirm that strategies including high-dose sequential therapy plus ASCT can give very good results in selected group of patients, and suggests that results achieved with conventional treatment plus HDS and ASCT are similar to those reported with the simple use of conventional therapy and ASCT. On final observation is that there is no apparent difference in using intensified therapy after CT in all cases or only in cases of persistent disease, even in higher-risk patients.

In conclusion, this study suggests that differences between patient selection methods in various reported studies probably have an impact on the interpretation of the different results.

## Conclusions

High-dose chemotherapy and autologous stem-cell transplantation has now become the standard care for eligible patients with recurrent, chemosensitive aggressive NHL. Primary refractory patients and resistant relapse are not good indications and should be considered group eligible for phase II studies.

There may also be a role in patients with partially responsive disease. However new and larger randomised studies are needed to clarify this question.

A challenge for lymphoma management is the evaluation of the role of high-dose therapy and ASCT as an initial treatment in aggressive NHL, identifying patients who will be not cured with standard therapy. A series of concurrent or retrospective analysis would indicate so-called "higher-risk patients", as defined by the IPI, as potential targets for intensified therapy. However, according to recent published data, the problem remains open to debate. Larger, randomised studies are necessary and welcome and this should be considered a high priority.

We hope that in the future, increased knowledge of the different biological properties of aggressive NHL and the addition of biological modifiers in the pre- and post- auto transplantation phase will enable us to improve the management of these categories of patients.

## Transplante autólogo de células progenitoras para pacientes com linfomas não Hodgkin agressivos

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### Resumo

O transplante autólogo de célula progenitora ou medula óssea (ATMO) tem demonstrado capacidade de superar resistência tumoral através da elevação da intensidade de dose de drogas disponíveis e radioterapia. ATMO foi inicialmente utilizado em LNH após recidiva em primeira linha ou refratários. ATMO tem demonstrado maior utilidade em condições clínicas mais favoráveis como na remissão parcial (RP), primeira remissão completa (RC) e como primeira linha após quimioterapia.

Quimioterapia de alta dose e ATMO se tornaram a terapêutica standard para pacientes elegíveis com LNH agressivo, recorrente e quimiosensível. Pacientes primariamente refratários e com recidiva resistente não são boas indicações e devem ser considerados como grupo elegível para estudos de fase II. Talvez, haja um papel do ATMO em pacientes parcialmente responsivos. Entretanto, novos e grandes estudos randomizados são necessários para esclarecer esta questão.

Um desafio para o manuseio dos linfomas é a definição da terapia de alta dose seguida do ATMO como terapêutica inicial para os LNH agressivos, identificando pacientes que não possam ser curados com terapêutica convencional. Uma série de estudos retrospectivos ou controlados parece indicar os chamados pacientes de "alto-risco", definido pela IPI como potencial alvo destas terapêuticas intensificadas. Entretanto, de acordo com dados publicados, o problema permanece aberto para debates. Estudos grandes e randomizados são necessários e bem vindos e devem ser considerados prioridade neste campo da ciência médica.

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**Palavras-chave:** Transplante autólogo de célula progenitora, linfomas não Hodgkin

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