High-dose therapy followed by stem cell transplantation in partial response after first-line induction therapy for aggressive non-Hodgkin’s lymphoma

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Summary

Patients with aggressive non-Hodgkin’s lymphoma who fail to achieve a complete remission (CR) with standard induction therapy have a poor prognosis with conventional-dose salvage therapy alone. Retrospective series have suggested that early introduction of high-dose salvage therapy with autologous stem cell transplantation (ASCT) may benefit partial-responder (PR) patients. However, two randomized studies (of 69 and 51 patients with partial clinical responses) failed to demonstrate any advantage of intensive therapy. By contrast, the GELA comparative study on 94 PR-patients (residual disease being histologically documented in 53 patients) suggested that high-dose therapy with ASCT improves survival. Interpretation of all these results is complicated by the heterogeneity of patient populations with respect to initial prognostic factors, induction regimens and, in particular, the criteria used to define partial response. Gallium CT scan and magnetic resonance imaging are now used to better explore residual masses. In the future, early restaging with these imaging techniques might be used to delineate patients who are likely to achieve CR from those who will fail to induction treatment and could be candidates for experimental treatments.

Key words: aggressive non-Hodgkin’s lymphoma, autologous stem cell transplantation, high-dose therapy

Introduction

The purpose of this review is to assess the outcome of patients with non-Hodgkin’s lymphoma (NHL) who achieve an incomplete response to front-line chemotherapy and to determine whether salvage treatment with high-dose therapy (HDT) followed by hematopoietic stem cell transplantation (HSCT) is useful in such patients.

Interpretation of the literature is complicated by many factors. First is the heterogeneity of the patient populations in and between published studies. Several studies have included patients with varying proportions of intermediate- and high-grade histologies and prognostic features. Other studies have reported on series of partial responders and non-responders (i.e., with refractory disease) mixed together. Primary treatment of aggressive NHL has varied from CHOP (or CHOP-like) regimens to third generation regimens. Finally and not marginally, the definition of partial response has varied among studies. Residual masses that remain after induction treatment often constitute a difficult diagnostic dilemma. When restaging with computed tomography (CT), many patients have residual masses that might reflect either persistent disease or fibrotic tissue without active lymphoma. Gallium scan and magnetic resonance imaging (MRI) are now proposed as valuable tools to explore further these residual masses.

Definition of partial response

Presence of a residual mass

A variety of criteria have been proposed to assess partial response but the most widely used are those ratified at the Cotswolds meeting [1] which define a partial response as "a decrease by at least 50% in the sum of the products of the largest perpendicular diameters of all measurable lesions". This definition might be reconsidered in the future using new imaging tests. Nevertheless with current available methods, the lack of pathological proof remains a crucial problem.

For more than a decade CT scan has been the gold standard for post therapy reevaluation of patients with NHL post therapy. Using chest X-rays and CT scans, Armitage et al. [2] showed ten years ago that the rapidity of response was a prognostic indicator and that durable remissions could be observed with fewer cycles in patients who achieved an early complete remission (CR).
In this series, 60% of the patients who did not achieve CR before cycle 5 of chemotherapy relapsed within the two-year period of observation. When CR was achieved after three cycles, the relapse rate was only 20%. However, evaluation by CT scan relies exclusively on changes in tumor size since there are no radiological characteristics that allow to differentiate between active lymphoma and fibrotic tissue. Therefore, size may be an imperfect indicator of the quality of response since the degree of tumor reduction differs among patients according to size of initial mass, location, histology, and type of treatment [3].

Due to its lack of accumulation in fibrotic tissue and its ability to localize in viable tumor cells $^{67}$Gallium scintigraphy may distinguish non active fibro-necrotic tumor from active disease in residual masses and in normal sized lymph nodes. The use of higher dose of $^{67}$Ga, modern equipment and single photon emission computed tomography (SPECT) have increased the accuracy of $^{67}$Ga scintigraphy for detection of residual disease after treatment.

A recent study [4] assessed the predictive value of early restaging gallium and CT scans in poor-prognosis patients with aggressive non-Hodgkin’s lymphoma. Thirty newly diagnosed patients with bulky advanced stage were treated with four cycles of a high-dose CHOP regimen. All patients had CT and Ga scans at baseline and following two and four cycles of therapy. The results of early (post-cycle 2) and final restaging were associated with clinical outcome. CT-documented rates of response and residual mass sizes were indistinguishable in complete responders who remained continuously disease-free or in those who subsequently progressed. By contrast, early Ga restaging delineated patients in continued CR (90% Ga-negative, 18 of 20 patients) from patients who relapsed from CR (25% Ga-negative, one of four patients) or progressed from PR (0% Ga-negative, zero of six patients) ($P = 0.000014$). On the basis of these data and of previous concordant results [5], the authors suggest that early restaging Ga scans should be used to tailor induction therapy in aggressive NHL patients.

Another recent study [6] evaluated the predictive value of CT scan and single-photon emission computed tomography (SPECT) gallium scanning in the disease-free survival of patients receiving HDC and autologous stem cell transplantation for NHL. CT and SPECT Ga scans were performed before transplantation and at day +100 after transplant. For patients with non follicular lymphoma, the conversion from a positive Ga scan pre-transplantation to a negative scan post transplantation was associated to a three-year failure-free survival of 48% compared with 19% if the Ga-scan remained abnormal after transplantation ($P = 0.008$). For patients with follicular NHL, the addition of SPECT Ga scan to CT scan did not add substantially to the evaluation of transplant outcome.

Magnetic resonance imaging can also help to distinguish inactive disease from viable tumor in residual masses. Indeed, the signal intensity of evolving lymphoma at MRI changes during the evolution of the process. The theoretical basis of signal change is as follows: active, untreated tumor tissue contains an excess of free water increasing the T2 signal intensity. With successful treatment, cellular elements and water content of the tumor are reduced while collagen and fibrotic stroma of the original tumor remain the main component, thus reducing the T2 signal intensity. In a study assessing the potential value of MRI [3], 34 patients (12 with NHL) with residual masses underwent MRI at sequential intervals, during and after therapy. Patterns of signal intensity suggestive of active and inextinct residual disease were compared to changes in tumor size. The signal intensity pattern was suggestive of persistent disease in 18 patients although tumor size was stable or even decreased. The MR imaging assessment of inactive disease was confirmed by MR follow-up in 15 of the 16 remaining patients. Because tumor size and signal intensity changes were not parallel in many cases, it was proposed that MRI should be used for monitoring residual masses in lymphoma.

Other studies have compared Ga scan and MRI [7–9]. Both methods seem to present similar sensitivity and specificity for assessing tumor activity in residual masses. However, it should be borne in mind that normalization of MRI probably takes place later than disappearance of $^{67}$Ga, as shown by several studies.

**Persistence of bone marrow involvement**

In the GELA study (see below), partial response was also defined by the presence of residual bone marrow involvement in patients with otherwise no residual masses after treatment. Infiltration had to be reduced as compared to initial involvement. In this series, 36 of 94 eligible patients were considered in partial response on the basis of this criteria. Topography of infiltration varied from nodular paratrabecular to diffuse pattern and cytology of involvement was mostly constituted of small cells. When discrete, the residual marrow involvement by lymphoma cells was further confirmed by immunophenotypic identification (CD20/CD3).

Is HDT followed by HSCT indicated in the setting of PR to primary therapy?

In a review article published in 1994, Haq et al. [10] summarized available data on conventional salvage chemotherapy regimens. These regimens yielded up to 60% overall response rates, but the 2y-disease-free survival rate did not exceed 10% to 30%. Among primary failures, PR did not appear as an adverse prognostic factor for the response to salvage therapy. In a few studies, CR was frequently induced when salvage therapy was started in PR-patients before disease progression. Although a CR can be obtained, there are few patients who experience long-term disease-free survival.
to conventional salvage therapy without bone marrow transplantation. However, interpretation of results of high-dose therapy followed by HSCT in this setting must take into account heterogeneity of the patient population and factors that have been shown to be of prognostic significance for HSCT especially chemosensitivity of disease.

**Retrospective studies**

Philip et al. [11] reported the results of 17 patients (11 children and six adults) who received HDT with autologous bone marrow transplantation after achieving a PR to induction treatment for aggressive lymphoma. Twelve patients had high-grade (10 Burkitt's and two lymphoblastic) and five had diffuse large-cell lymphoma. Ten patients had surgically proven active disease in the abdomen, two had active disease in the bone marrow, and five persistent neurologic symptoms. Thirteen of 17 patients (75%) remain alive and disease-free, with a median observation time of two years. These results compare favorably to the results observed in patients with a PR to front-line therapy who did not receive HDT and HSCT [9].

Other non-randomized studies [12-15] also suggested on small series that early introduction of dose-intensive salvage therapy could benefit patients with a PR and requires testing in randomized clinical trials.

**Randomized studies**

Two recently published series did not demonstrate any advantage of high-dose therapy over a conventional chemotherapeutic approach. Verdonck et al. [16] compared five additional courses of CHOP chemotherapy versus early high dose chemo-radiotherapy (cyclophosphamide and total body irradiation) in 69 randomized patients, who had lymphoma-negative marrow, considered as ‘slow-responders’ after three courses of CHOP. Criteria of partial response were unusual, here defined as a reduction by at least 25% of the sum of the largest tumor diameters. At four years, the rates of event free survival and survival did not significantly differ between the two treatment groups (53% vs. 41% and 85% vs. 56%, respectively). The Italian Study group [17] evaluated the efficacy of dexamethasone, cisplatin, and cytarabine (DHAP) chemotherapy as compared with high-dose BEAC in 51 randomized patients with a clinical partial response after two thirds of a conventional front-line therapy. A consolidation radiation therapy on the sites of residual disease was planned for these patients. Partial response was defined as a response between 50% and 80% of the initial manifestations. At 55 months, progression-free and overall survival did not statistically differ between the groups (52% vs. 73% and 59% vs. 73%, respectively). No definite conclusion can be drawn from these two studies since the number of randomized patients is low and it remains difficult to avoid the bias of patients in clinical partial response due to residual non-active masses.

**The GELA comparative study**

Among 759 eligible patients enrolled in the LNH87-2 protocol [18] between 1987 and 1991, 101 patients (13%) achieved a partial response after induction treatment. The induction treatment randomly compared four courses of two anthracyclin-containing regimens given every two weeks: the LNH84 induction regimen, with doxorubicin 75 mg/m² (ACVB) or mitoxantrone 12 mg/m² (NCVB). Data are available on 94 patients in partial response. Baseline characteristics of these patients were the following: median age: 43 years, large cell subtype: 60%, stage III-IV: 83%, tumoral mass ≥ 10 cm: 71%, bone marrow involvement: 48%, LDH > 1N: 53%. In this study PR was defined as a 50% to 75% reduction in tumor volume with or without persistence of residual bone marrow involvement. In 55 patients, pathologic evaluation of residual disease was performed and lymphoma was documented in 53 patients (bone marrow 36, abdominal mass 13, peripheral node one, skin one, pleura one). Of the 94 PR-patients, two patients were not treated (one patient refusal and one death related to hemorrhagic disease after splenectomy); 32 patients received the LNH84 consolidative phase (ifosfamide plus etoposide, asparaginase, cytarabine); 49 received various salvage regimens based on one or two major drugs (mitoxantrone, ifosfamide and etoposide in 16; methotrexate in 13; ifosfamide, etoposide and cytarabine in five; cytarabine, cisplatin in three; other types of treatments in 12). Of these 49 patients, one patient received an allogenic bone marrow transplantation with a sibling donor and 33 patients were treated with intensive therapy followed by autologous HSCT (marrow: 26 patients, peripheral stem cell: seven patients) after a median time from initial diagnosis of six months. The intensive regimens were: BEAM (n = 13) or BEAC (n = 7), CBV (n = 5), cyclophosphamide with or without etoposide and total body irradiation (n = 7). With a median follow-up of 82 months, overall five-year event-free survival and survival were 42% (95% confidence interval (95% CI): 32%-52%) and 50% (95% CI: 40%-60%, Figure 1),

![Figure 1. Overall survival of the 94 PR-patients.](image-url)
respectively. Event-free survival of autotransplanted patients was 62% (95% CI: 44%-80%) as compared to 30% (95% CI: 20%-40%) for conventionally treated patients ($P = 0.003$, Figure 2). Survival of the autotransplant group was also better: 65% (95% CI: 49%-81%) as compared to 40% (95% CI: 28%-52%, $P = 0.005$, Figure 3). This comparative study, although retrospective, suggest that dose-intensive salvage therapy should be proposed early to patients who achieve PR after induction treatment.

### References


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