REVIEW ARTICLE

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Treatment of Aggressive Non-Hodgkin's Lymphoma with Chemotherapy in Combination with Filgrastim

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Abstract

Non-Hodgkin's lymphoma (NHL) is one of the ten most common cancers in the developed world. The incidence has increased significantly over the past two decades and it is a particular burden in patients over the age of 60 years. The gold standard for primary treatment of aggressive NHL is combination chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP). Haematological growth factors, such as granulocyte colony-stimulating factor (G-CSF), can be used to ameliorate chemotherapy-induced neutropenia, thus facilitating delivery of chemotherapy at the planned dose intensity. The International Prognostic Index is able to identify high-risk patients who are unlikely to be cured with standard primary chemotherapy. In these patients, the use of dose-intensive therapy, including high-dose chemotherapy with stem cell support, is being evaluated as potential primary therapy. Stem cell transplantation is currently the treatment of choice for patients with relapsed NHL or those with chemosensitive refractory disease. Autologous peripheral blood stem cells mobilised into the circulation by G-CSF help achieve rapid haematological reconstitution and are now the preferred source of stem cells over bone marrow for this form of therapy. G-CSF is also used to support allogeneic transplantation, which exerts a therapeutic graft-versus-lymphoma effect. Administration of G-CSF following autologous or allogeneic peripheral blood stem cell transplantation accelerates neutrophil recovery.

1. Introduction

Non-Hodgkin's lymphoma (NHL) is one of the ten most frequent cancers in the developed world. In the US, it is the second most common cause of cancer-related death among men aged 15 to 34 years and the third leading cause of cancer death in men aged 35 to 54 years.[1]

The incidence of NHL has increased significantly over the past two decades, with the most marked increase seen in patients over the age of 60 years. Data from the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) programme, which collects data from population-based registries in five states and four standard metropolitan statistical areas, showed an annual increase of 3.5% in the incidence of NHL from 1973 to 1990, and 0.8% between 1990 and

1995. Mortality also increased significantly during both time periods (1.8 and 1.9%, respectively). During 1990 to 1995, only the annual increase seen in lung cancer mortality (2.1%) was greater than the rise in NHL mortality.[2]

2. Classification of Non-Hodgkin's Lymphoma (NHL)

The NHLs are a heterogeneous group of lymphoproliferative disorders involving malignant monoclonal populations of B, T or natural killer (NK) lymphocytes. They originate in lymphoid tissue (lymph nodes or spleen), but can spread to other organs. The development of a universal classification system for the NHLs has been an ongoing challenge. Until recently, the Working Formulation (table I) has been the standard used by most clinicians. Although this nicely divides patients into categories of indolent and aggressive disease, there have been a large number of newly recognised syndromes such as mantle cell and marginal zone lymphomas that did not fit into the working formulation. The latest classification that has been adopted is the Revised European American Lymphoma (REAL) system proposed by the International Lymphoma Study Group in 1994.[3] This system (table II) encompasses all of the lymphoid neoplasms and essentially lists all diseases with distinct clinicopathological characteristics.

Table I. Working Formulation classification system

Low grade
Small lymphocytic
Plasmacytoid
Follicular, small cleaved cell
Follicular mixed, small cleaved and large cell
Intermediate grade
Follicular, large cell
Diffuse, small cleaved cell
Diffuse mixed, small and large cell
Diffuse, large cell
High grade
Immunoblastic, large cell
Lymphoblastic
Small noncleaved cell
Burkitt's
Non-Burkitt's

Table II. Revised European-American classification of lymphoid neoplasms (From Harris NL, Jaffe ES, Stein H, et al. A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. Blood 1994; 84: 1361-92.[3] Copyright© American Society of Hematology, used by permission.)

B-cell neoplasms
I. Precursor B-cell neoplasm
Precursor B-lymphoblastic leukaemia/lymphoma
II. Peripheral B-cell neoplasms
1. B-cell chronic lymphocytic leukaemia/prolymphocytic leukaemia/small lymphocytic leukaemia
2. Lymphoplasmacytoid lymphoma/immunocytoma
3. Mantle cell lymphoma
4. Follicle centre lymphoma, follicular
Provisional cytological grades: I (small cell), II (mixed small and large cell), III (large cell)
Provisional subtype: diffuse, predominantly small cell type
5. Marginal zone B-cell lymphoma, extranodal mucosa-associated lymphoid tissue type (with or without monocytoid B cells)
Provisional subtype: nodal marginal zone lymphoma (with or without monocytoid B cells)
Provisional entity: splenic marginal zone lymphoma (with or without villous lymphocytes)
6. Hairy cell leukaemia
7. Plasmacytoma/plasma cell myeloma
8. Diffuse large B-cell lymphoma[a]
Subtype: primary mediastinal (thymic) B-cell lymphoma
9. Burkitt's lymphoma
10. Provisional entry: high-grade B-cell lymphoma, Burkitt-like[a]
T-cell and putative natural killer-cell neoplasms
I. Precursor T-cell neoplasm
Precursor T-lymphoblastic lymphoma/leukaemia
II. Peripheral T-cell and natural killer-cell neoplasms
1. T-cell chronic lymphocytic leukaemia/prolymphocytic leukaemia
2. Large granular lymphocyte leukaemia
T-cell type
Natural killer-cell type
3. Mycosis fungoides/Sézary syndrome
4. Peripheral T-cell lymphomas, unspecified[a]
Provisional cytological categories: medium-sized cell, mixed medium and large cell, large cell, lymphoepitheloid cell
Provisional subtype: hepatosplenic γδ T-cell lymphoma
Provisional subtype: subcutaneous panniculitic T-cell lymphoma
5. Angioimmunoblastic T-cell lymphoma
6. Angiocentric lymphoma
7. Intestinal T-cell lymphoma (with or without enteropathy associated)
8. Adult T-cell lymphoma/leukaemia
9. Anaplastic large cell lymphoma, CD30+, T- and null-cell types
10. Provisional entry: anaplastic large cell lymphoma, Hodgkin's-like

a These categories are thought to be likely to include more than one disease entity.

There are two broad categories of NHL within the system: B-cell derived and T/NK-cell derived. Within the B-cell and T-cell groups, diseases are further separated into precursor- and peripheral-cell–derived types. Distinct clinical entities are defined on the basis of morphology, phenotype, molecular characteristics and clinical behaviour. The clinical utility of the REAL classification system was established in a study involving 1403 NHL patients at nine centres worldwide.[4] The World Health Organization (WHO) has adopted a slightly modified version of the REAL scheme as the classification for lymphoid malignancies.[5]

For practical purposes, NHL can be described as aggressive or indolent. Aggressive lymphomas progress rapidly without therapy, but a reasonable proportion of patients can achieve a cure with intensive combination chemotherapy; overall survival at 5 years is 50 to 60%. In contrast, indolent lymphomas have a median survival of up to 10 years, but are generally not considered curable. Aggressive lymphomas include diffuse large B-cell lymphomas, diffuse large B-cell lymphoma of the mediastinum, anaplastic large cell lymphoma and some peripheral T-cell lymphomas. Diffuse large B-cell lymphoma is the most common form of aggressive NHL. Precursor B- and T- lymphoblastic leukaemia/lymphomas, adult T-cell leukaemia/lymphoma associated with HTLV-1 infection and Burkitt's lymphoma are classified as highly aggressive lymphomas and are treated in a different manner.

Treatment of NHL depends on the histological type and stage of disease. Patients with NHL are often assessed according to the Ann Arbor staging scheme or modifications of this system (table III). The number, size and location of involved lymph node regions and extralymphatic organs determine the staging.

Table III. Ann Arbor staging system

Stage	Description[a]
I	Involvement of a single lymph node region or a single extralymphatic organ or site (IE)
II	Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localised involvement of an extralymphatic organ or site (IIE)
III	Involvement of lymph node regions on both sides of the diaphragm (III) or localised involvement of an extralymphatic organ or site (IIIE) or spleen (IIIS) or both (IIISE)
IV	Diffuse or disseminated involvement of one or more extralymphatic organs with or without associated lymph node involvement. Bone marrow and liver involvement

a Identification of the presence or absence of symptoms should be noted with each stage designation: A = asymptomatic; B = fever, sweats, weight loss >10% of bodyweight.

2.1 International Prognostic Index for Aggressive NHL

Although staging may determine some basic treatment approaches, the more recently described International Prognostic Index (IPI) is used to categorise patients with aggressive NHL, in terms of their chance of survival, into low-, low intermediate-, high intermediate- and high-risk disease groups.[6] This index incorporates five independent variables: patient age (<60 *vs* >60 years), performance status (ECOG 0-1 *vs* 2-4), lactate dehydrogenase (LDH) level (normal *vs* elevated), number of extranodal sites (0-1 *vs* 2-4), and disease stage (I-II *vs* III-IV). Patients aged <60 years are classified into risk groups according to the age-adjusted IPI, which considers only disease stage, performance status and LDH level. Shipp[6] performed a seminal study establishing the utility of the IPI index. The study involved 2031 patients with aggressive NHL. Overall survival at 5 years after diagnosis in patients treated with doxorubicin-based therapy was 73% in IPI low-risk patients; 51% in low intermediate-risk patients; 43% in the high intermediate-risk patients; and only 26% in the high-risk group. High-risk patients have less chance of achieving a complete remission and are more likely to relapse than low-risk patients.

3. Primary Treatment for Aggressive NHL

3.1 Combination Chemotherapy with Cyclophosphamide, Doxorubicin, Vincristine and Prednisone

Combination chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) remains the gold standard for treatment of aggressive NHL. Although, third-generation therapies, which involve the addition of bleomycin, methotrexate and/or etoposide and cytarabine, appeared to improve results in phase II trials, a phase III trial by Fisher et al.[7] showed no improvement in disease-free or overall survival among patients with aggressive NHL randomised to CHOP, m-BACOD (methotrexate with leucovorin rescue, bleomycin, doxorubicin, cyclophosphamide, vincristine and dexamethasone), MACOP-B (methotrexate with leucovorin rescue, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin), or ProMACE-CytaBOM (prednisone, doxorubicin, cyclophosphamide and etoposide, then cytarabine, bleomycin, vincristine and methotrexate with leucovorin rescue). Complete response rates were 44, 48, 51 and 56%, respectively, and disease-free survival rates after 3 years of follow-up were 41, 41, 46 and 46%. Since CHOP is better tolerated than the other regimens, it has remained the standard of care for patients with aggressive NHL.

3.2 Combination Chemotherapy with Cyclophosphamide, Doxorubicin, Vincristine and Prednisone + Rituximab

There has been new interest in the use of rituximab, an anti-CD20 monoclonal antibody, in combination with CHOP as front-line therapy. Rituximab was first shown in the setting of low-grade NHLs to improve complete response rates. Czuczman and colleagues[8] reported results from 40 patients with low-grade or follicular B-cell NHL. The overall response rate was 95% (complete response 22 of 40 patients and partial response 16 of 40 patients), and 74% of evaluable patients remained in remission for a median of 29 months after therapy.

The GELA (Groupe d'Etudes des Lymphomes de l'Adulte) recently published a randomised study comparing CHOP + rituximab versus CHOP alone in 328 patients over the age of 60 years with previously untreated stage II-IV diffuse large B-cell lymphoma.[9] The complete response rate (76 *vs* 63%, p = 0.005), 2-year event-free survival (57 *vs* 38%, p < 0.001) and overall 2-year survival (70 *vs* 57%, p < 0.01) significantly favoured the CHOP + rituximab arm (figure 1). Further analysis of these patients, revealed that the survival advantage of adding rituximab to CHOP was even apparent in both the low- and high-risk (IPI) patients. Ongoing trials are attempting to confirm these results.[10]

3.3 Role of Colony-Stimulating Factors (CSFs) in the Primary Treatment of Aggressive NHL

Colony-stimulating factors (CSFs) are a family of glycoprotein haematopoietic growth factors that regulate the differentiation of myeloid cell lines. One such compound is granulocyte colony-stimu-

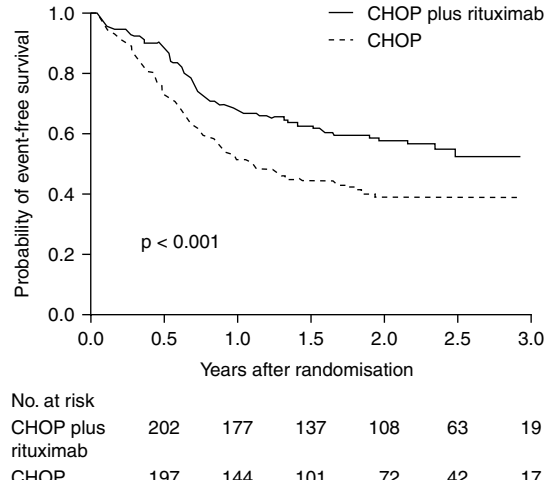


Fig. 1. Event-free survival among 399 patients assigned to chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) or with CHOP plus rituximab. (Reproduced from Coiffier B, Lepage E, Briere J, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med 2002; 346: 235-42.[9] Copyright© 2002 Massachusetts Medical Society. All rights reserved.)

lating factor (G-CSF), which selectively stimulates proliferation and differentiation of neutrophil precursors. Granulocyte-macrophage colony-stimulating factor (GM-CSF) is a growth factor that stimulates proliferation of neutrophils, eosinophils and monocytes/macrophages. Recombinant forms of these CSFs are commercially available; for example, Amgen's filgrastim (Amgen Inc., Thousand Oaks, California, USA) is a human form of G-CSF that is synthesised in bacteria, and sargramostim is a human form of GM-CSF that is synthesised in yeast. Clinical uses of G-CSF in aggressive NHL are outlined in table IV.

3.3.1 Reducing Neutropenia and Permitting Delivery of the Planned Chemotherapy Dose

Cytotoxic chemotherapy in patients with aggressive NHL is hampered by severe myelosuppression and subsequent susceptibility to infection, especially in older patients. Early studies show that adjunctive use of CSFs reduces the incidence of neutropenia and febrile neutropenia and decreases the need for dose reductions or delays in patients with aggressive NHL receiving cytotoxic chemotherapy.

In a randomised study, 80 patients with aggressive NHL were treated with a weekly regimen of VAPEC-B (vincristine, doxorubicin, prednisolone, etoposide, cyclophosphamide and bleomycin), with (n = 41) or without (n = 39) G-CSF at a dosage of 230 μg/m^2/day.[11] Neutropenia was significantly less frequent among patients treated with G-CSF (37 *vs* 85%, p = 0.00001), as were neutropenia with fever (22 *vs* 44%, p = 0.04) and the need for dose reductions (10 *vs* 33%, p = 0.01). Overall, patients treated with G-CSF were able to receive greater chemotherapy dose intensity as a result of fewer dose delays and dose reductions, compared with patients who did not receive G-CSF. With the small numbers of patients enrolled in the study, no difference was observed between the groups in overall or disease-free survival. Other trials have reported that reduced dose intensity is associated with a poorer outcome.[25,26]

3.3.2 Dose Intensification

Adjunctive use of G-CSF can enable dose-intensified chemotherapy regimens to be given safely.[12,15] It is hoped that using this strategy will increase complete response rates and ultimately lead to improved survival in patients receiving intensive therapy. Preliminary results from a prospective, randomised trial of dose-intensified CHOP have recently been reported in an abstract.[18] Patients over the age of 60 years were randomised to receive six cycles of standard CHOP every 3 weeks (CHOP21), CHOP plus etoposide (CHOEP21) or either regimen administered every 2 weeks (CHOP14 or CHOEP14). Patients receiving therapy every 2 weeks began G-CSF starting on day 4 until neutrophil recovery. Interim results have been reported on 807 patients (median age 67 years). After a median follow-up of 40 months, time to treatment failure (53 *vs* 43%, p = 0.03) and overall survival (64 *vs* 49%, p = 0.04) were significantly better in the dose-intensi-

Table IV. Clinical uses of granulocyte colony-stimulating factor (G-CSF) in aggressive non-Hodgkin's lymphoma

Indication	Outcome
Primary prophylaxis of chemotherapy-induced neutropenia	Reduces the incidence of neutropenia, febrile neutropenia and hospitalisation for infectious complications after cytotoxic chemotherapy. Reduces the need for dose delays/reductions and facilitates delivery of the planned chemotherapy dose[11,12] Facilitates administration of full-dose chemotherapy in elderly patients[13,14]
Dose intensification of chemotherapy	Facilitates dose escalation and shortened treatment intervals of myelosuppressive drugs.[15-17] Dose intensification has been associated with a survival benefit in elderly patients[18]
Mobilisation of PBSCs	Transplantation of G-CSF-mobilised PBSCs achieves more rapid haematological recovery than BMT.[19,20] G-CSF can also be used to mobilise allogeneic PBSCs[21,22]
Post-transplant administration of G-CSF	Accelerates haematological recovery and reduces infectious complications after autologous[23] and allogeneic transplantation[24]

BMT = bone marrow transplant; **PBSCs** = peripheral blood stem cells.

fied CHOP14 group than in those receiving standard CHOP21. The improvement was more marked in patients who had elevated LDH. No improvement was seen by the addition of etoposide.

3.3.3 Patients Aged >65 Years

Older NHL patients, who form a substantial portion of the NHL population, are less likely than younger patients to receive full-dose chemotherapy. A retrospective survey[27] compared older and younger patients by use of the average relative dose intensity (ARDI), which is determined by dividing the ratio of actual dose to duration by the ratio of standard dose to duration. ARDIs were calculated for received and planned doses. As compared with younger patients, those aged >65 years were significantly more likely to have a planned ARDI ≤80% and a received ARDI ≤80%. This suggests that the worse outcome seen in older patients may be due, in part, to administration of suboptimal chemotherapy doses.

One potential reason for attenuation of chemotherapy dose in older patients is that the risk of myelosuppression increases with age. As dose reductions may compromise the effectiveness of chemotherapy, prophylactic use of haematopoietic growth factors is recommended in elderly patients.[28] Studies have shown that use of primary prophylactic G-CSF facilitates administration of full-dose chemotherapy and enables elderly patients to achieve clinical outcomes similar to those in younger patients. A study by Zinzani and colleagues[13] demonstrated that G-CSF prophylaxis in elderly patients with aggressive NHL, receiving VNCOP-B chemotherapy (cyclophosphamide, mitoxantrone, vincristine, etoposide, bleomycin, and prednisone), significantly lowered the incidence of neutropenia. The complete response rate in this study was 58%, similar to that seen historically in younger patients with aggressive NHL. Five-year relapse-free and overall survival rates were 65 and 49%, respectively. Another study in elderly (>60 years) NHL patients found that the need for treatment delays was reduced in those who received G-CSF with all of their cycles of CHOP.[14] In that study, 47 of 50 patients received G-CSF either prophylactically or in response to neutropenia. Overall, the dose intensity achieved for cyclophosphamide and doxorubicin was 90% of ideal CHOP dosage. Complete response rates were 100, 81, 85 and 36% in the low-, low intermediate-, high intermediate- and high-risk groups, respectively. Five-year actuarial overall survival rates in this study were comparable to those previously seen in patients aged ≤60 years in the IPI study.[6]

3.4 High-Dose Chemotherapy with Stem Cell Support as Primary Treatment of Aggressive NHL

Since CHOP chemotherapy is capable of curing only approximately half of unselected patients with aggressive NHL, there is significant room for improvement in treatment outcome. The IPI index identifies patients at higher risk of relapse who might be candidates for more intensive support. One such approach would be to identify higher risk patients and treat them with high-dose sequential (HDS) chemotherapy and autologous stem cell support. HDS chemotherapy involves sequential administration of each cytotoxic drug at very high doses, followed by a final intensified phase with stem cell infusion. CSFs are given during the initial high-dose phase to reduce myelotoxicity (by accelerating neutrophil recovery). In addition, CSFs, such as cytotoxic drugs, stimulate mobilisation of haematopoietic progenitors into the peripheral blood. These peripheral blood stem cells (PBSC) can then be collected by leukapheresis, cryopreserved and reinfused after myeloablative chemotherapy to promote rapid reconstitution of the haematopoietic system.

Several trials have attempted to address whether the addition of high-dose chemotherapy followed by autologous stem cell support as upfront therapy can improve the overall survival for patients with aggressive NHL. These trials differ substantially in their design and patient population, and thus their conclusions. Two reviews have recently been published.[29,30] The International Consensus Conference on high-dose therapy with haematopoietic

stem-cell transplant in aggressive NHL reconvened to determine whether sufficient data had become available to address important questions regarding the role of stem cell support in this setting.[29] For each question concerning stem-cell support in aggressive NHL, the jury made a positive or negative recommendation or pointed out that there were too few data to make a recommendation. The merit of the evidence supporting each recommendation was also assessed consistently with standard approved criteria. Committee members felt that the benefit of high-dose therapy with stem cell support still needs to be determined in newly diagnosed patients and they were optimistic that the role of high-dose therapy with stem cell support in this population would be clarified in ongoing randomised clinical trials.

The American Society for Blood and Marrow Transplantation has completed an evidence-based review of the role of cytotoxic therapy with haematopoietic stem cell transplantation in the therapy of diffuse large-cell B-cell NHL.[30] Recommendations for the treatment of newly diagnosed patients are summarised in table V.

3.4.1 Primary Refractory Disease

Patients with primary refractory NHL represent a very difficult subset to treat. Fortunately, true refractoriness is relatively rare. Kewalramani et al.[33] examined the outcomes of 85 patients who underwent second-line chemotherapy with ICE (ifosfamide, cisplatin, etoposide) following failure with first-line induction therapy. Patients were classified as induction partial responders (IPR) or induction failures (IF) on the basis of their response to initial therapy. Forty-three (51%) had chemosensitive disease with no difference in response observed between those who were IPR or IF. Of 42 patients who ultimately underwent autologous bone marrow transplant (ABMT), the 3-year overall survival and event-free survival were 53 and 44%, respectively, suggesting that even patients with induction failure can be cured with transplantation, as long as they remain chemosensitive. An analysis of the autologous blood and marrow transplant registry study came to similar conclusions.[34]

3.4.2 Early Partial Responders

In one small Dutch trial, 69 patients who had a partial response after three cycles of CHOP were randomised to bone marrow transplant (BMT) versus additional CHOP.[35] There were no differences in disease-free or overall survival between the groups. The sample size, however, was too small and the number of higher-risk patients too few to allow any firm conclusions on the role of transplantation in this subgroup.

The Italian NHL study group randomised 124 patients to receive induction chemotherapy alone or followed by transplantation.[36] Patients in the chemotherapy-only arm who obtained a less than complete response underwent BMT. Patients in the transplant arm proceeded regardless of their initial

Table V. Treatment recommendations by disease response and International Prognostic Index (IPI) risk

Indication for SCT	Treatment recommendation	Level of evidence	Reference[a]	Comments
As high-dose sequential therapy in untreated patients with high-intermediate or high IPI risk	Effective treatment	Evidence obtained from at least one properly randomised, controlled trial	Gianni et al.[31]	
As high-dose sequential therapy in untreated patients with low or low-intermediate IPI risk	Inadequately evaluated treatment and recommended for comparative study	Evidence obtained from at least one properly randomised, controlled trial	Milpied et al.[32]	Only 45% of the patients had low or low-intermediate IPI risk; included 55% patients with high-intermediate or high IPI risk

a The references listed represent the highest level of evidence used to make the treatment recommendation.

SCT = haematopoietic stem cell transplantation.

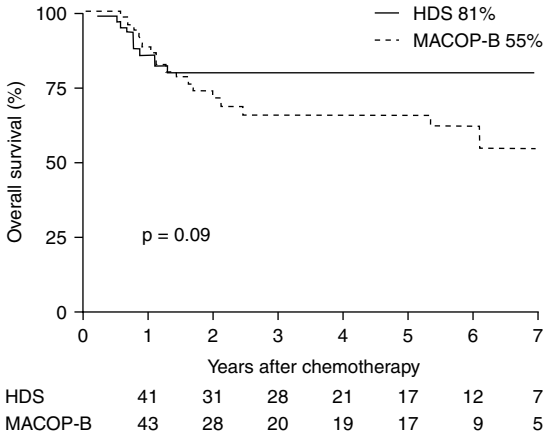


Fig. 2. Kaplan-Meier plot of overall survival for 48 patients initially assigned to high-dose sequential therapy (HDS) and 50 assigned to MACOP-B.[31]The initial number of patients in complete remission and at risk for relapse was 46 for HDS and 35 for MACOP-B (methotrexate with leucovorin rescue, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin). The median follow-up was 55 months. The number of patients at risk is shown below each timepoint. Percentages at right are for overall survival at 7 years. (Reproduced from Gianni AM, Bregni M, Siena S, et al. High-dose chemotherapy and autologous bone marrow transplantation compared with MACOP-B in aggressive B-cell lymphoma. N Engl J Med 1997; 336: 1290-97.[31] Copyright© 1997 Massachusetts Medical Society. All rights reserved.)

response to chemotherapy. With median follow-up of 42 months, there was no difference in the 6-year overall survival rates. When outcome was analysed on the basis of IPI risk, there was a trend in favour of the group receiving transplantation.

In this patient population, the benefit of BMT is yet to be determined.

3.4.3 High-Risk Patients in Complete Response

Several trials have examined the role of ABMT in patients with poor-prognosis NHL. Gianni et al.[31] randomised patients to MACOP-B for 12 weeks versus HDS therapy and autologous transplantation. At a median 55 months follow-up, the complete response rate was 96% in the HDS group, compared with 70% in the MACOP-B group (p = 0.001). Rates of freedom from disease 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) were all significantly superior in the HDS group. Overall survival (figure 2) at 7 years favoured the HDS group (81 *vs* 55%, p = 0.09).

Haioun et al.[37] performed the final analysis of the LNH87-2 trial, which randomised patients between sequential chemotherapeutic consolidation using methotrexate, ifosfamide, etoposide asparaginase and cytarabine versus intensive consolidation followed by autologous transplantation. They retrospectively identified patients who were IPI high/intermediate or high risk. Of the 451 patients with high-risk disease, 277 went into a complete response and 236 were randomised to transplant or further chemotherapy. The transplant arm had significantly higher disease-free (55 *vs* 39%, p < 0.02) and overall survival rates (64 *vs* 49%, p < 0.04) than the sequential chemotherapy arm (figure 3 and figure 4). Although this trial was not designed to prospectively answer this question, since

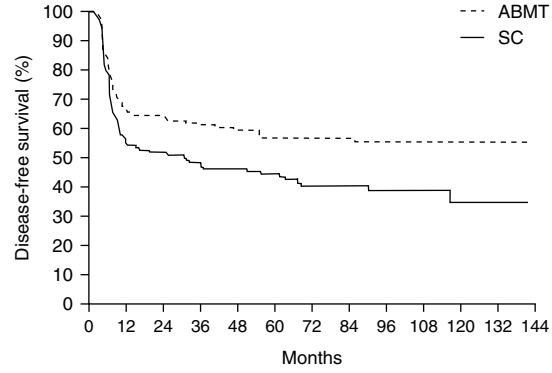
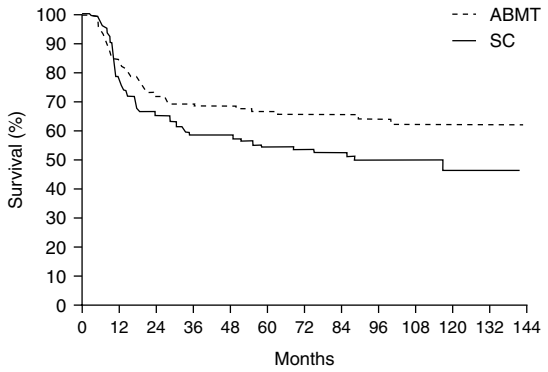


Fig. 3. Estimated disease-free survival according to randomised consolidation procedure for the high/intermediate- and high-risk patients. Sequential chemotherapy (SC): patients at risk, n = 111; 8-year estimate, 39%; autologous bone marrow transplantation (ABMT): patients at risk, n = 125; 8-year estimate, 55% (p = 0.02). (Reproduced from Haioun C, Lepage E, Gisselbrecht C, et al. Survival benefit of high-dose therapy in poor-risk aggressive non-Hodgkin's lymphoma: final analysis of the prospective LNH87-2 protocol – a Groupe d'Etude des Lymphomes de l'Adulte study. J Clin Oncol 2000; 18: 3025-30.[37] 2000 Lippincott Williams & Wilkins©.)



No. of evaluable pts at each timepoint

ABMT	80	76	72	69	63	56	46	35	20	13	6
SC	60	54	49	46	43	36	28	19	10	6	0

Fig. 4. Estimated survival according to randomised consolidation procedure for the high/intermediate- and high-risk patients. Sequential chemotherapy (SC): patients at risk, n = 111; 8-year estimate, 49%; autologous bone marrow transplantation (ABMT): patients at risk, n = 125; 8-year estimate, 64% (p = 0.04). (Reproduced from Haioun C, Lepage E, Gisselbrecht C, et al. Survival benefit of high-dose therapy in poor-risk aggressive non-Hodgkin's lymphoma: final analysis of the prospective LNH87-2 protocol – a Groupe d'Etude des Lymphomes de l'Adulte study. J Clin Oncol 2000; 18: 3025-30.[37] 2000 Lippincott Williams & Wilkins© .)

it was launched before the description of the IPI stratification, it is strongly suggestive that patients at high risk benefit from more intensive therapy.

Bouabdallah et al.[38] reviewed data from a single centre on 126 consecutively treated patients who received either standard chemotherapy or high-dose therapy with stem cell support. It was not a randomised trial; however, patients had similar clinical characteristics and it also showed a statistically significant difference in overall and disease-free survival in favour of patients who underwent autologous transplantation.

In 1997, the US National Comprehensive Cancer Network published practice guidelines for the various forms of NHL.[39] These guidelines recommend upfront treatment with high-dose chemotherapy and stem cell support, in the context of clinical trials, for high intermediate- and high-risk patients with advanced aggressive NHL.

There are currently several active randomised phase III trials in this patient population. The results of these trials should clarify the role of dose-intensive therapy followed by transplantation in this group of patients.

4. Treatment of Relapsed/Refractory Aggressive NHL

4.1 Autologous Stem Cell Transplantation

Despite high complete response rates with standard therapy, a substantial proportion of patients with aggressive NHL still relapse. Salvage chemotherapy regimens in relapsed/refractory patients typically incorporate drugs that are not used widely as first-line therapy, such as etoposide, cytarabine, cisplatin, ifosfamide, methotrexate and idarubicin.[40,41] Salvage regimens produce a second complete response in 25 to 35% of relapsed patients, but these responses are not generally maintained long term.

Patients who demonstrate disease responsiveness to salvage therapy are candidates for autologous stem cell transplantation.

ABMT has now been shown in a randomised trial to be the treatment of choice for patients with relapsed responsive NHL. The Parma study[42] randomised patients who had chemosensitive disease to receive further chemotherapy (n = 54) plus radiotherapy, or to radiotherapy plus intensive conditioning chemotherapy and ABMT (n = 55). Patients randomised to the transplant arm had significantly higher complete response rates (84 *vs* 44%). At 5 years, event-free survival (46 *vs* 12%, p = 0.001) and overall survival (53 *vs* 32%, p = 0.038) were significantly superior in transplanted patients (figure 5 and figure 6). This trial laid the foundation for the use of high-dose therapy with stem cell rescue in patients with NHL.

4.2 Allogeneic Transplantation

Autologous stem cell transplantation has generally been used in the treatment of relapsed/refractory NHL. There are some patients, however, in whom this approach may not be feasible (inability

to collect stem cells, diffuse marrow disease) or in whom autologous transplantation does not appear to be an effective strategy (primary nonresponsive disease). An alternative strategy is to use stem cells harvested from an human leucocyte antigen-related or unrelated donor. This approach has the advantage of obtaining cells that are clear of potential contamination with lymphoma cells as well as collecting stem cells that have not been exposed to multiple cycles of chemotherapy. More importantly, whereas autologous transplantation is effectively a method to deliver very high doses of chemotherapy, allogeneic transplantation also relies on the immune system to produce a 'graft-versus-lymphoma effect'.[43-48] This effect is responsible for the reduced relapse rates seen after allogeneic marrow transplantation.

Despite lower relapse rates, the role of allogeneic transplant has been somewhat limited, primarily because of the significantly higher early mortality associated with these transplants.

Nonmyeloablative chemotherapy with allogeneic stem cell transplantation, sometimes referred to as 'minitransplantation', represents an attempt to harness the graft-versus-lymphoma effect while minimising the toxicity typically seen after standard allogeneic transplantation. Instead of myeloablative doses of chemotherapy that are traditionally used in allogeneic transplantation, patients receive lower doses of chemotherapy designed primarily to allow sufficient immunosuppression so that the allogeneic stem cells are able to 'take' and prevent graft rejection. The premise is that the new immune system will produce a graft-versus-lymphoma effect once engraftment has been accomplished.[49-51] Toxicity associated with the intensive chemotherapy regimen is reduced, and morbidity and mortality rates are lower than with conventional allogeneic transplantation.

One particularly interesting strategy uses an initial autologous transplant (designed to debulk the disease) followed by nonmyeloablative allogeneic transplantation designed to take advantage of the graft-versus-lymphoma effect.[52] Such therapeutic strategies continue to remain investigational at this time but may ultimately lead to higher cure rates even in patients with more advanced disease states.

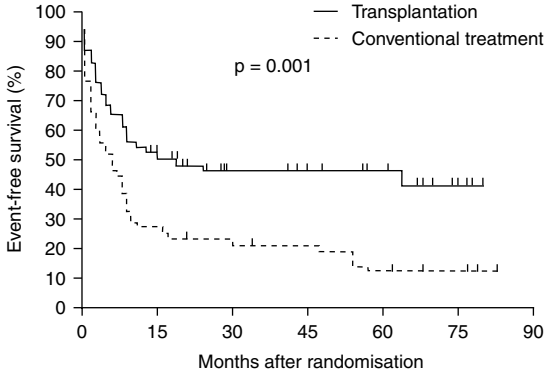


Fig. 5. Kaplan-Meier curves for event-free survival of patients in the transplantation and conventional-treatment groups.The data are based on an intention-to-treat analysis. Tick marks represent censored data. (Reproduced from Philip T, Gugliemi C, Hagenbeek A, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy of chemotherapy-sensitive non-Hodgkin's lymphoma. N Engl J Med 1995; 333: 1540-45.[42] Copyright© 1995 Massachusetts Medical Society. All rights reserved.)

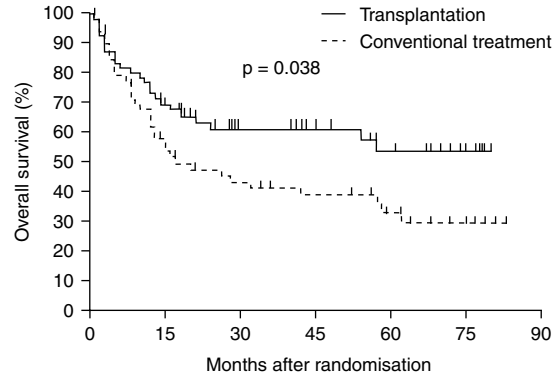


Fig. 6. Kaplan-Meier curves for overall survival of patients in the transplantation and conventional-treatment groups.The data are based on an intention-to-treat analysis. Tick marks represent censored data. (Reproduced from Philip T, Gugliemi C, Hagenbeek A, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy of chemotherapy-sensitive non-Hodgkin's lymphoma. N Engl J Med 1995; 333: 1540-45.[42] Copyright© 1995 Massachusetts Medical Society. All rights reserved.)

5. Role of CSFs in Stem Cell Transplantation

As discussed previously, high-dose chemotherapy with autologous or allogeneic stem cell rescue plays a crucial role in the treatment of relapsed/refractory NHL. Haematopoietic growth factors, primarily G-CSF, are intimately involved in this treatment process.

5.1 Use of CSFs to Mobilise Stem Cells for Autologous Transplantation

Administration of growth factors, alone or in combination with chemotherapy, stimulates mobilisation of stem cells into the peripheral blood. Randomised trials have demonstrated that mobilised peripheral blood progenitor cells (PBPCs) have more rapid haematological recovery than marrow cells.[19,20] Additional trials have shown economic benefits in using PBPCs versus marrow cells, and this technique has virtually replaced the use of bone marrow cells for autologous transplantation.[53]

5.1.1 Comparing Different Mobilising Regimens

G-CSF and GM-CSF are the most commonly used growth factors to mobilise PBSCs. To date, there are few data available from prospective, randomised trials comparing the relative effectiveness of these compounds. However, results from one randomised study comparing G-CSF (6 μg/kg/day), GM-CSF (250 μg/m^2/day) or sequential GM-CSF then G-CSF following myelosuppressive chemotherapy were recently reported.[54] Patients in the study had lymphoma, multiple myeloma or breast cancer and were undergoing autologous PBSC transplantation. They received growth factors from the day of completion of myelosuppressive chemotherapy until the final day of apheresis. CD34+ yield per apheresis was significantly higher in patients treated with G-CSF alone, compared with GM-CSF alone. Furthermore, patients in the G-CSF group had significantly faster recovery of neutrophils, a lower incidence of fever, a lower rate of hospitalisation, and less antibiotic treatment than the GM-CSF group. These parameters were comparable between the G-CSF alone and sequential GM-CSF/G-CSF groups. The results of this study suggest that G-CSF is a better mobilisation agent than GM-CSF.

Combinations of various growth factors have also been studied. The combination of G-CSF and stem cell factor has shown significantly improved results over G-CSF alone in heavily pretreated NHL or Hodgkin's disease patients.[55] Sufficient CD34+ yield could be achieved with fewer leukaphereses in patients treated with the combination mobilising regimen. Haematological recovery was similar in the two groups.

At present, clinical practice is to mobilise stem cells following chemotherapy with growth factor support. G-SCF is used in the majority of cases, with combination therapy being reserved for patients who are poor mobilisers.

5.2 Use of CSFs to Mobilise Stem Cells for Allogeneic Transplantation

G-CSF can also be used safely to mobilise PBSCs in healthy donors for allogeneic PBSC transplantation.[56] Although there was some initial concern that there would be a higher rate of acute graft-versus-host disease (GVHD) in patients transplanted with PBPCs, recent trials have shown not only is this not the case, but patients receiving PBPC grafts appear to have better long-term disease-free survival than patients who have received marrow alone.[57-59]

A recent article suggests that G-CSF-mobilised bone marrow results in comparable engraftment, with less severe acute GVHD and a lower incidence of chronic GVHD than in patients who receive mobilised PBSCs.[60]

Interestingly, one study has looked at the experiences of donors randomised to donate marrow or PBSC. Patients were mobilised using G-CSF 16 μg/kg with collections beginning on the fifth day, or underwent standard bone marrow harvest. Sixty-nine donors enrolled in the trial. Although the peak symptoms and level of pain did not differ

between the two groups, the duration appeared to be slightly longer in the marrow harvest arm.[61]

These data suggest that mobilisation of PBSC or marrow cells will be superior to unmobilised marrow. The best choice at present is unclear and further research is necessary to better define the ideal stem cell product.

5.3 Post-Transplant Administration of CSFs

Administration of G-CSF after infusion of mobilised autologous PBSCs accelerates neutrophil recovery and shortens the duration of hospitalisation in relapsed/refractory lymphoma patients.[23] Similarly, post-transplant administration of G-CSF is beneficial after allogeneic PBSC transplantation. Bishop and colleagues[24] performed a double-blind study, in which patients were randomised to receive G-CSF (10 μg/kg/day) or placebo following infusion of allogeneic mobilised PBSCs. The time to neutrophil recovery was significantly shorter in the G-CSF-treated patients (11 *vs* 15 days, $p = 0.0082$), but there were no significant between-group differences in terms of platelet recovery or acute GVHD.

6. Conclusions

The incidence of NHL has increased markedly over the past two decades, and it is a particular problem within the older population. Despite this, for 25 years the standard upfront therapy for NHL has remained unchanged.

The field, however, has not been stagnant. We now have agents that target surface antigens, which are present on most B-cell lymphomas. One of these, rituximab, has recently been shown to increase the remission rates and survival in patients with newly diagnosed aggressive NHL. While these results are being confirmed by ongoing clinical trials, other agents have been approved which use monoclonal antibodies conjugated to yttrium-90 and iodine-131, delivering radiation directly to the site of disease.

The development of the IPI, which stratifies patients into low-, low intermediate-, high intermediate- or high-risk disease, has been a major step forward. This stratification can predict patients in whom standard therapy is likely to fail and who may benefit from more intensive upfront therapy.

In the last 10 years, we have learned that high-dose therapy and stem cell support is the treatment of choice for patients with relapsed chemosensitive disease. The use of growth factors has revolutionised the field of stem cell transplantation. We have progressed from using marrow support alone, and patients being neutropenic for 20 to 30 days, to routinely having periods of neutropenia of <10 days with the use of mobilised PBPC and post-transplant growth factor support. The mortality is now sufficiently low for there to be ongoing clinical trials examining the role of stem cell transplantation for patients at high risk of relapse based on their IPI scores.

It is unclear which therapy is best for patients who are resistant to chemotherapy, although allogeneic marrow transplantation may play an important role and is the subject of numerous ongoing clinical trials. Nonmyeloablative allogeneic transplantation is a newer modality designed to minimise toxicity and retain the graft-versus-lymphoma effect. The role it will play in the therapy of aggressive NHL is as yet unclear.

Other exciting therapies, including additional monoclonal antibodies, antisense oligonucleotides versus bcl 2 and gene therapy, suggest that soon we will have new standards of care for an old disease.

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