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Economic evaluation of chemotherapy

Treatment of non-Hodgkin's lymphoma

George Dranitsaris
Department of Pharmaceutical Services, Ontario Cancer Institute/Princess Margaret Hospital, 610 University Avenue, Toronto, Ontario M5G 2M9, Canada. Tel: (+1) 416 946-4577; Fax: (+1) 416 946-2014.

Non-Hodgkin's lymphoma (NHL) is the most common type of lymphoid malignancy that affects over 40 000 people in North American alone. The difficulty associated with NHL is correctly assigning patients into homogenous histologic subtypes. Appropriate classification is of paramount importance because the multiple subgroups are associated with distinct clinical outcomes. Current anticancer therapy for this heterogenous disease includes chemotherapy, radiation, cytokine administration and dose-intensive myeloablative antineoplastic treatments followed by autologous bone marrow rescue. With the optimal management strategy, approximately 50% of patients with aggressive NHL can achieve prolonged disease-free survival and even clinical cures. This article will review current therapies for NHL, and discuss some recent advances in the clinical application of prognostic factors, cytokines and the role of transplantation.

Key words: Non-Hodgkin's lymphoma, therapy.

Introduction

In the US alone, malignant lymphomas are the seventh most common cause of cancer death. In 1992, approximately 41 000 new cases were diagnosed and there were approximately 19 400 deaths from the disease.[1] The two major subtypes include Hodgkin's disease and non-Hodgkin's lymphoma (NHL). Of the two, the latter malignancy is by far the more prevalent and represents approximately 85% of all lymphoma diagnoses.[2] Of particular concern is the rising incidence of NHL. One epidemiological study reported that between 1973 and 1989, the incidence of NHL increased by nearly 60% in the US, one of the largest single increases of any cancer.[3] Fortunately, one of the major successes of oncology in the past two decades has been the ability to cure certain subtypes of NHL with appropriate anticancer therapy. Given that patients with more aggressive disease are usually offered chemotherapy with a curative intent, this review will focus on these patient subgroups.

Correspondence to G Dranitsaris

Subgroups of NHL

Since the objective of treating many lymphomas is cure rather than palliation, accurate diagnosis and staging is required. In order to facilitate the placement of patients into histologically homogeneous groups, the National Cancer Institute of the US sponsored a major classification project in the early 1980s.[4] The result was a classification system that allowed the assignment of a treatment and prognosis to each patient subgroup (Table 1). Regardless, considerable controversy about the classification of lymphomas remains to this day. In order to address this issue, the International Lymphoma Study Group proposed a revised European-American classification of lymphoid neoplasms (REAL).[5] However, it is still too early to know if this revised system will be widely adopted by the hematology community.

Based on experimental evidence accumulated to date, the intermediate- and high-grade lymphomas are considered to be curable. Despite median survival estimates that exceed 5 years, the vast majority of low-grade lymphomas are not curable. However, there is a very small subgroup of patients with localized disease that could be cured with radiation therapy.[6]

An Ann Arbor staging system has also been developed for NHL.[7] Stage IA or IB disease is characterized by a single nodal region or a single extranodal site. Patients with IIA or IIB NHL typically have two or more nodal regions or an extranodal site and regional nodal involvement on the same side of the diaphragm. NHL that is staged as IIIA or IIIB disease usually has lymphatic involvement on both sides of the diaphragm. Finally, stage IVA and IVB are the most aggressive forms of the disease, and are associated with liver or bone marrow involvement.[7]

Table 1. Characteristics of the major histologic subtypes of NHL[4,6]

Histologic subtypes	Cases (%)	Distribution by stage (%)				Bone marrow involvement (%)	Median survival (years)	Cure with chemotherapy
		I	II	III	IV			
Low grade								
small lymphocytic	4	3	8	8	81	71	5.8	no
follicular small cleaved	22	8	10	16	66	51	7.2	no/rare
follicular mixed	8	15	12	28	46	30	5.1	uncertain
Intermediate grade								
follicular large	4	15	12	15	58	34	3.0	probable
diffuse small cleaved	7	9	19	12	60	32	3.4	probable
diffuse mixed	7	19	26	13	42	14	2.7	yes
diffuse large	20	16	30	10	44	10	1.5	yes
High grade								
immunoblastic	8	23	29	16	33	12	1.3	yes
lymphoblastic	4	7	20	2	72	50	2.0	yes
small non-cleaved	5	13	21	9	57	14	0.8	yes

The remaining 12% of NHL cases consists of a miscellaneous subgroup of lymphoma-related diseases.

Typically, the 'B' indicates the presence of symptoms such as night sweats, a 10% loss in body weight or fevers. Patients in category 'A' do not have these symptoms.

Prognostic factors associated with response and long-term survival

In the past decade, several groups have applied statistical techniques to identify important prognostic factors for complete response and long-term survival.[8-10] The clinical features identified as being correlated with disease response and survival reflect tumor growth rates and invasive potential (Table 2). The five dominant prognostic variables associated with poor outcomes are age more than 60 years, stage III or IV disease, disease involvement at two or more extranodal sites, poor performance status and abnormal serum lactate dehydrogenase (LDH) levels.

An international collaboration consisting of 16 institutions from the US, Europe and Canada participated in the Non-Hodgkin's Lymphoma Prognostic Factors Project. The objectives of this initiative were to link disease response and overall survival with the clinically important prognostic factors.[11] After the initial statistical screening, the final prognostic model consisted of age ($\leqslant 60$ versus >60), disease stage (I or II versus III or IV), extranodal involvement ($\leqslant 1$ site versus >1 site), ECOG performance status (0 or 1 versus $\geqslant 2$) and serum LDH levels ($\leqslant 1 \times$ normal versus $>1 \times$ normal). The results of the analysis identified four groups of aggressive lymphoma with 5-year survival rates at 73% (group I), 51% (group II), 43% (group III) and 26% (group IV), respectively (Table 3).

Table 2. Prognostic factors associated with disease outcome[10,11]

Age (<60 versus $\geqslant 60$ years)
Patient performance status (ECOG 0 or 1 versus $\geqslant 2$)
Disease stage (localized I/II versus advanced III/IV)
Number of nodal and extranodal disease sites
B symptoms (present versus absent)[a]
Mass size (<10 versus $\geqslant 10$ cm)
Bone marrow involvement (yes versus no)
Serum LDH (normal versus twice normal)
Serum β_2-microglobulin (<3 versus $\geqslant 3$ mg/l)
Serum albumin (<35 versus $\geqslant 35$ g/l)

[a]Night sweats, 10% weight loss or fever.

Treatment of localized disease

Patients with only one or two adjacent sites of disease and with tumors less than 10 cm in diameter are good candidates for clinical cures with appropriate therapy. The bulk of patients investigated have been subtypes of intermediate- and high-grade lymphoma (Table 1). The primary method of treatment involves radiation with or without adjuvant chemotherapy. In cases of diffuse large cell lymphoma in Ann Arbor stage I, it has been reported that approximately 50% of patients can be cured with radiation therapy alone.[12] However, the addition of chemotherapy has improved cure rates to beyond 75%.[13]

Adjuvant chemotherapy in patients with localized disease usually contains several agents in combination

with doxorubicin. One of the most commonly used adjuvant regimens is the CHOP protocol (cyclophosphamide, doxorubicin, vincristine and prednisone). In patients with stage I or non-bulky stage II disease, the current treatment standard is the administration of three or four courses of CHOP, followed by radiation therapy.[14] However, in those patients who refuse radiotherapy because of side effects, a full six cycles of chemotherapy may be given as an alternative. Contrary to this, patients who are advanced in age with a poor ECOG performance status or those who refuse chemotherapy, radiotherapy alone may be offered.[7]

Treatment of advanced lymphoma

Patients diagnosed with advanced stage low-grade lymphoma are generally considered non-curable. Asymptomatic patients with no complications from their lymphoma do not require immediate therapy and only need to be monitored closely. In some cases, spontaneous remissions have also been reported.[15] However, the vast majority of these patients are treated with radiation, systemic chemotherapy or a combination of the two.[16] There is also evidence to suggest that patients treated with more aggressive immunochemotherapy have improved response durations and longer overall survival. In one randomized trial, patients with aggressive low- or intermediate-grade lymphoma received either CHOP or CHOP in combination with interferon (IFN)-α.[17] Following eight cycles of treatment, the investigators reported identical response rates (86% in both groups). However, the duration of response and overall survival was statistically superior in patients who received IFN-α following the chemotherapy.[17]

Table 3. Survival and probability of relapse according to the prognostic factors project[11]

Patient classification	Complete response (%)	5-year survival (%)
Group I: low risk[a] (no. of risk factors=0 or 1)	87	73
Group II: low intermediate (no. of risk factors=2)	67	51
Group III: high intermediate (no. of risk factors=3)	55	43
Group IV: high (no. of risk factors=3)	44	26

[a]Risk factors in the final model included: age (≤60 versus >60), disease stage (I or II versus III or IV), extranodal involvement (≤1 versus >1 site), ECOG performance status (0 or 1 versus ≥2) and serum LDH levels (≤1 × normal versus >1 × normal).

Patients with intermediate/high-grade, stage III/IV disease NHL can be cured with combination chemotherapy (Table 4). Among the first generation protocols, CHOP offered a 6-year disease-free survival in approximately 32% of patients with minimal toxicity and was therefore considered the standard of therapy.[18] In the 1980s, several single-center phase II trials reported increased complete remission and improved survival rates with second- and third-generation chemotherapy regimens which consisted of six to eight drugs.[19,20] However, when these regimens were compared to standard CHOP under randomized trial conditions, complete response and disease-free survival were identical to CHOP.[21,22] Furthermore, the newer protocols were associated with increased drug toxicity and higher treatment costs. Consequently, CHOP is still considered the standard first-line therapy for patients with advanced stage NHL.[21,22]

The role of dose intensity

On a theoretical basis, maximizing the dose intensity of certain primary agents (e.g. cyclophosphamide and doxorubicin) should correlate with improved patient response and prolonged disease-free survival. Several retrospective studies in patients with aggressive advanced stage lymphoma have shown just that.[23-25] In spite of these findings, prospective randomized comparative trials have failed to support the hypothesis that maximal dose intensity improves patient survival.[21,26] However, it is important to keep in mind that the survival benefit due to maximal dose intensity may be marginal and the trials conducted to date have not had the statistical power to detect significant differences. In order to adequately address the issue of dose intensity, a randomized trial with sufficient sample size and designed to specifically address this outcome is required. Hematopoietic growth factors should be added to the experimental arm to deliver the highest possible dose of chemotherapy.

Cytokines in NHL

The cytokines are a series of regulatory hormones that stimulate the proliferation, differentiation and activation of cells involved in hematopoiesis and mature leucocyte function. Given the advances in recombinant DNA technology, several cytokines are now available commercially. These include hematopoietic growth factors such as granulocyte macrophage colony stimulating factor (GM-CSF) and granulocyte colony stimulating factor (G-CSF). These agents are

Table 4. Randomized trials comparing first-line chemotherapy in advanced NHL

Regimen	Complete response (%)	Percent surviving (duration)		Reference
		Disease-free survival	Overall survival	
C-MOPP	44	28 (3 years)	31 (36 months)	78
BACOP	51	48 (3 years)	49 (36 months)	
COPA	48	–	–	79
COPA-B	49	–	–	
COPA-BP	42	–	–	
CHOP	61	–	35 (36 months)	80
MEV	24	–	30 (36 months)	
CHOP	51	–	48 (5 years)	21
m-BACOD	56	–	49 (5 years)	
CHOP	63	–	45 (30 months)	81
MACOP-B	45	–	63 (30 months)	
CHOP	58	49 (5 years)	43 (5 years)	82
ProMACE-CytaBOM	62	56 (5 years)	41 (5 years)	
F-MACHOP	76	84 (28 months)	84 (32 months)	83
MACOP-B	63	80 (28 months)	64 (32 months)	
ProMACE-MOPP	74	54 (6 years)	53 (6 years)	84
ProMACE-CytaBOM	86	69 (6 years)	69 (6 years)	
m-BACOD	57	60 (58 months)	57 (58 months)	85
m-BNCOD	57	55 (58 months)	52 (58 months)	
ProMACE-CytaBOM	58	64 (2 years)	72 (27 months)	86
MACOP-B	63	60 (2 years)	71 (27 months)	
CHOP	44	41 (3 years)	54 (3 years)	22
m-BACOD	48	46 (3 years)	52 (3 years)	
ProMACE-CytaBOM	56	46 (3 years)	50 (3 years)	
MACOP-B	51	41 (3 years)	50 (3 years)	

Abbreviations: C-MOPP: cyclophosphamide, vincristine, procarbazine and prednisone; BACOP; bleomycin, doxorubicin, cyclophosphamide and vincristine; COPA: cyclophosphamide, vincristine, prednisone and doxorubicin; CHOP: cyclophosphamide; doxorubicin, vincristine and prednisone; MEV: methotrexate, cyclophosphamide and vincristine; MACOP-B: methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone and bleomycin; ProMACE-CytaBOM: prednisone, doxorubicin, cyclophosphamide, etoposide, cytarabine, bleomycin, vincristine and methotrexate.

indicated for the prevention of febrile neutropenia in patients receiving highly myelosuppressive chemotherapy.[27,28] In the past few years, the utility of growth factors in mobilizing progenitor cells for autologous and allogeneic marrow transplantation has also been realized.[29,30] The role of transplantation in the treatment of NHL will be dealt with in the subsequent section of this review.

Other agents whose therapeutic potential has been investigated include IFN-α, interleukin (IL)-2 and IL-3.[31-33] The first cytokine evaluated clinically was IFN-α. Early trials suggested that IFN-α as a single agent was inactive against intermediate-grade, high-grade and bulky tumors.[34,35] However, clinical benefit was demonstrated in low-grade malignant NHL, provided that the tumour mass is low.[36,37] The synergistic effects of IFN-α when combined with chemotherapy in low-grade tumors have also been established.[17,38,39]

Early *in vitro* studies evaluating IL-2 indicated that it may have a role in NHL because of its ability to activate monocyte, T lymphocyte and natural killer cell-mediated antineoplastic mechanisms.[31,40] However, clinical trials involving IL-2 failed to show activity in patients with refractory or relapsing lymphoma.[41,42] Only a minor effect was evident in patients with low-grade disease.[42] Recently, there have been some

reports that IL-2 following autologous or allogeneic transplantation reduces the incidence of relapse, secondary to its ability to increase the concentration of circulating natural killer cells.[43,44] However, these results have yet to be confirmed under randomized trial conditions.

The introduction of GM-CSF and G-CSF into the clinical arena has removed neutropenia as the dose-limiting toxicity in NHL patients receiving intensive chemotherapy. In these patients, thrombocytopenia is now becoming the treatment-limiting toxicity. Phase II trials have suggested that IL-3 stimulates the production of thrombocytes, and also has an effect on granulocytes and macrophages.[45,46] Studies examining IL-3 in combination with lineage-specific hematopoietic growth factors (e.g. G-CSF) have also been completed.[47,48] However, a detailed discussion of these studies will be covered in another paper in this special issue.

Salvage therapies in patients with refractory or recurrent disease

It has been estimated that between 5 and 10% of patients with advanced lymphoma will not achieve a complete response (CR) following first-line therapy.[10] Considering patients who achieve a partial response (PR), encouraging results have been reported with intensive chemotherapy supported with autologous bone marrow rescue.[49] In those unfortunate patients who do not achieve a CR or PR, enrollment into a clinical trial should be considered.

Among those patients who achieve a CR following first-line therapy, up to 40% will develop recurrent disease within the first 2–3 years.[50,51] For these patients, numerous salvage regimens incorporating drugs that are typically not used during first-line therapy have been developed (Table 5). Unfortunately, only 20–35% of patients achieve a second CR with salvage therapy and the majority of these responders relapse within 1 year.[52] As a result, increased attention has been placed on the role of autologous bone marrow transplantation (ABMT) in patients with relapsed or recurrent disease.

Transplantation in NHL

High-dose chemotherapy followed by an ABMT has the potential for prolonged disease-free survival and even cures in patients with NHL.[53–55] What makes this option even more attractive is that recent advances in cancer supportive care have now reduced treatment-related mortality to less than 5%.[53] There have also been technical advances in the harvesting of progenitor cells. An alternative source of progenitor cells to the bone marrow is the peripheral blood. Progenitor cells normally circulate in the blood in low numbers. Following priming with growth factors (G-CSF and GM-CSF), the concentration of these cells in the peripheral blood is substantially enhanced. With increased numbers, it is then possible to collect a sufficient quantity of cells (via leukopheresis) that are subsequently reinfused in order to re-establish hematopoiesis following myeloablative chemotherapy.

The advantages of peripheral blood progenitor cell transplantation (PBPC) over ABMT are that it significantly reduces the time for neutrophil and platelet recovery, which contributes to a lower overall risk of infection, reduced need for platelet transfusions and shorter hospital stays.[56] Another benefit of using PBPC in auto-transplantation is that high-dose chemotherapy can now safely be offered to those patients with bone marrow involvement at the time of harvest. Prior to this, the majority of these patients would have been treated with allogeneic transplantation (allo-BMT) as an alternative.

Table 5. Salvage protocols for patients with relapsed NHL

Regimen	No. of patients	CR (%)	Duration of CR (months)	Two-year survival (%)	Reference
IMVP-16	38	37	12	20–25	87
MIME	123	32	15	20–25	52
DHAP	74	32	24	25	88
ESHAP	88	38	20	⩾30	89
CEPP(B)	69	36	NA	30–35	90
Mitoxanthrone	100	9	6	10–15	91
MIV	52	42	NA	NA	92

Abbreviations: IMVP-6: ifosfamide, methotrexate and etoposide; MIME: methyl-gag, ifosfamide, methotrexate and etoposide; DHAP: dexamethasone, cytarabine and cisplatin; ESHAP: etoposide, solumedrol, cytarabine and cisplatin; CEPP(B): cyclophosphamide, etoposide, procarbazine, prednisone and bleomycin; MIV: mitoxanthrone, ifosfamide and etoposide.

Allogeneic versus autologous transplantation

There are no published randomized trials comparing HLA-matched transplants versus autologous stem cell transplantation. However, several non-randomized trials reported that allo-BMT reduces the risk of relapse by approximately 50%, compared to ABMT.[57,58] The lower relapse rate following allo-BMT has been attributed to an immunologic 'graft-versus-lymphoma' effect and the absence of tumor cell contamination of the stem cell product. Unfortunately, the lower relapse rates have been offset by higher treatment-related mortality due to graft-versus-host-disease (GVHD) and infectious complications. The overall result has been no statistically significant difference in disease-free and overall survival between the two procedures.[57-59] Therefore, the primary role of allo-BMT has been in NHL patients with extensive bone marrow and/or peripheral blood involvement.[60]

The role of autologous transplantation in NHL

The majority of evidence supporting transplantation has been in patients with relapsed or refractory high- or intermediate-grade disease.[61,62] Autologous transplantation is now considered standard therapy in such patients. However, this may not be the only role of ABMT in patients with aggressive NHL. Subsequent analyses of prognostic factors have suggested that patients with recurrent disease who were responsive to conventional chemotherapy achieved better results than patients who were refractory to primary treatment.[63,64] Given these findings, a possible role of ABMT may be for patients who achieve a first CR following conventional chemotherapy.

The largest randomized trial to evaluate this hypothesis was conducted by a French/Belgian collaborative group.[65] Following first-line therapy, 541 patients in first CR were randomized to sequential consolidation therapy or to intensive cyclophosphamide, carmustine and etoposide (CBV) chemotherapy followed by an ABMT. At 5 years follow-up, the investigators were unable to find significant differences in disease-free or overall survival between the two arms. However, a subgroup analysis on high-risk patients (two or three risk factors) did reveal a statistically significant benefit in 5-year disease-free survival (59 versus 39%: p=0.01) with ABMT. The investigators concluded that dose-intensive chemotherapy followed by ABMT should be considered for high-risk patients who achieve a CR after induction treatment.[65]

Additional evidence supporting upfront dose-intensive therapy followed by stem cell rescue was recently provided by Gianni *et al.*[66] Ninety-eight patients with newly diagnosed high-risk diffuse large cell and mixed lymphoma were randomized to either MACOP-B or to intensive chemotherapy followed by PBPC transplantation. The investigators reported a superior event-free (76 versus 49%: p=0.004) and overall survival (81 versus 55%: p=0.09) in the transplant group.

Another important issue is the role of ABMT in patients who achieve only a PR following first-line chemotherapy. In another randomized trial conducted by Verdonck *et al.*,[67] 106 patients with PRs and lymphoma-negative marrow after three courses of CHOP were randomized to continue another five CHOP cycles or to high-dose chemoradiotherapy followed by ABMT. At 4 years follow-up, disease-free, event-free and overall survival did not differ between groups. These results do not support the early administration of high-dose chemoradiotherapy and ABMT in this patient subgroup. Similar outcomes were also obtained in an Italian randomized study.[68]

An economic evaluation was subsequently conducted by Uyl-de Groot *et al.*,[69] who concluded that the substitution of ABMT for sequential CHOP in slow responders is more expensive and provides less quality-adjusted life years (i.e. is economically dominated by sequential CHOP). In this situation, the respective Canadian and US guidelines for economic evaluations recommend that such a treatment not be adopted by society.[70,71]

One patient subgroup in which the role of ABMT remains unknown is in low-grade aggressive lymphoma. Since the median age at diagnosis of these patients is approximately 60 years of age and the median survival is 7 years, clinicians have been reluctant to offer transplantation to this population, thus explaining the lack of randomized comparative trials. As a result, it has been recommended that high-dose chemotherapy followed by ABMT or PBPC in patients with low-grade advanced stage lymphoma should only be investigated as part of a clinical trial.[72]

New treatments

Several new agents have shown activity in some of the NHL subtypes.[73] In non-randomized clinical trials involving relapsed or refractory patients, single-agent fludarabine exhibited response rates between 30 and 55%.[74,75] In combination with other agents such as mitoxanthrone, fludarabine also demonstrated im-

pressive response rates in heavily pretreated patients. In one phase II trial, 48 patients with recurrent low-grade NHL received a combination of fludarabine, mitoxanthrone and prednisone.[76] At the completion of therapy, the complete and partial response rates were 35 and 48%, respectively. Others areas of investigation are currently focusing on immunotoxins or radioisotopes combined with monoclonal antibodies directed against specific lymphoma antigens.[77] Notwithstanding, the efficacy of these newer agents has to be confirmed through randomized comparative trials.

Economic considerations

Given the fiscal challenges faced by many cancer treatment centers around the world, the efficient use of the institutional drug budget is a practical way to save costs. In the case of chemotherapy for NHL, there are many ways to achieve this objective. As an illustration, it was demonstrated that standard first line CHOP chemotherapy is clinically equivalent and less toxic compared to the second generation protocols such as MACOP-B, PROMACE-CYTABOM and BACOP.[21,22] In addition, CHOP is available at a substantially lower acquisition cost relative to the other regimens (CHOP=$471 versus MACOP-B=$3452, PROMACE-CYTABOM=$530 and BACOP=$684; all Canadian $).

As a final consideration, CHOP chemotherapy is less myelosupressive compared to the newer protocols with rates of neutropenic fever that are less than 5%.[21,22] Therefore, expensive agents like filgrastim are generally not required following a cycle of CHOP. If neutropenia becomes a problem in later cycles, then a dose delay of 1 week or lower doses of filgrastim (150 μg/day) would usually correct the neutropenia.[93,94] In summary, there are many opportunities for the cost-effective use of drugs in the treatment of NHL. This includes the re-establishment of older and less toxic protocols, and the appropriate use of growth factors. The development of institutional practice guidelines using an evidence-based medical approach may help achieve these objectives.

Conclusions

NHL is a disease of increasing prevalence that affects over 40 000 people in Canada and the US alone. In the past two decades, major advances in the treatment of this disease have been made. Provided that tumor types are classified appropriately and that the optimal therapeutic regimen is offered, approximately 50% of patients with advanced NHL can achieve prolonged disease-free survival and clinical cures. However, there is still considerable room for improvement, particularly in certain high-risk patient subgroups with aggressive disease. Additional clinical trials are required to identify the optimal role of transplantation, cytokine therapy and the many new agents that are currently under investigation. Patience, focus and continued clinical research is needed to overcome this disease.

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