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*Perspectives in Cancer Research*

# Current Status and Perspectives in the Treatment of Non-Hodgkin's Lymphomas*

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THE non-Hodgkin's lymphomas (NHL), a term introduced into clinical language 15 yr ago, have undergone considerable re-evaluation in the past decade.

The NHL represent a complex group of neoplastic diseases with variable natural history and widely divergent patterns of response to treatment. Their classification still remains a highly controversial issue. For many years the Rappaport classification, originally published in 1957 and revised in 1966, was favoured by many clinicians because of its simplicity and good clinical correlation in therapeutic trials [1]. In the Rappaport classification the presence or absence of a nodular pattern was the primary discrimination, the secondary being the predominant cell type. However, in the last decade many new and somewhat more sophisticated lymphoma classifications have been proposed in an attempt to incorporate more recent advances in immunopathology [2–5]. Because of the resulting confusion, the National Cancer Institute has proposed a working formulation for clinical usage [6]. The formulation is not a new classification for NHL "but a tabulation system intended to ensure that the diagnostic terms in the classification can be coded to a uniform nomenclature . . ." [7]. This tabulation was based on the degree of biological aggressiveness of the tumour, which was deduced from the survival curves: low-grade (median survival 6 yr); intermediate-grade (3.5 yr); and high-grade (1.3 yr). Meanwhile, a good and practical classification remains a goal of great importance. This need is also expressed in the most recent literature, where correlations between treatment and different histologic subtypes are sought [8–11]. Only a thorough understanding of basic data such as cytogenetics, kinetics and immunologic cell markers will provide a rational basis for an optimal classification. Recent achievements in these fields indicate that progress can be expected in the near future [12–14].

For the sake of simplicity we divide the lymphomas in indolent and aggressive or unfavourable forms, knowing that patients treated for their indolent lymphomas may develop an aggressive type in up to 30% of cases [15]. The incidence of transformation of untreated, indolent lymphomas is unknown.

For indolent lymphomas, and in spite of conflicting data, following evidence is gradually appearing (using the Rappaport classification):

(a) The Stanford group has reported observation of 44 asymptomatic patients whose treatment was initially deferred. The treatment-free period was almost 5 yr for patients with diffuse well-differentiated (DLWD) and nodular poorly differentiated (NLPD) lymphocytic lymphomas [15]. Abstention from therapy appears still permissible since there are as yet no convincing data in favour of a more aggressive approach [16]. When treatment is needed the length of time required to induce complete remission may be a useful therapeutic guide: the duration of treatment required to induce complete remission is shortest for whole-body irradiation (6–12 weeks), intermediate for combination chemotherapy (6–12 months) and longest for daily alkylating-agent (12–24 months). Some authors favour, however, an early aggressive approach in all nodular lymphomas [17].

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*This paper is dedicated to Prof. G. Martz on the occasion of his 60th birthday.

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*Table 1. Results of combination chemotherapy in patients with advanced diffuse histiocytic lymphoma*

| Regimen | % CR | Median survival (months) all | CR only | Reference | Year |
|---|---|---|---|---|---|
| CHOP | 51 | 21 | (33) | [27] | 1980 |
| BACOP | 48 | 14 | >17 | [32] | 1976 |
| COMLA | 55 | — | >33 | [29] | 1980 |
| M-BACOD | 77 | 38 | * | [33] | 1983 |
| ProMace-MOPP | 74 | >48 | † | [34] | 1983 |
| COP-Blam | 73 | >23 | >26 | [30] | 1982 |

*Actuarial survival analysis predicts that 80% of CR patients will survive 60 months.
†Actuarial survival analysis predicts that 82% of CR patients will survive 48 months.

*Table 2. Newer regimens of chemotherapy used in the treatment of NHL*

| | | |
|---|---|---|
| **CHOP** | | Ref. [27] |
| Cyclophosphamide | 750 mg/m² i.v., day 1 | |
| Doxorubicin | 50 mg/m² i.v., day 1 | |
| Oncovin (vincristine) | 1.4 mg/m² i.v. (max. 2 mg), day 1 | |
| Prednisone | 100 mg p.o., days 1–5 | |
| | (repeat every 2–3 weeks) | |
| **COMLA** | | Ref. [29] |
| Cyclophosphamide | 1.5 g/m² i.v., day 1 | |
| Oncovin (vincristine) | 1.4 mg/m² i.v. (max. 2 mg), days 1, 8 and 15 | |
| Methotrexate | 120 mg/m² i.v., days 22, 29, 36, 43, 50, 57, 64 and 71 | |
| Leucovorin | 25 mg/m² p.o. every 6 hr × 4 doses, 24 hr after the methotrexate | |
| Cytosine arabinoside | 300 mg/m² i.v., days 22, 29, 36, 43, 50, 57, 64 and 71 | |
| | (repeat twice weekly after a 2-week rest period) | |
| **BACOP** | | Ref. [32] |
| Bleomycin | 5 mg/m² i.v., days 15 and 21 | |
| Doxorubicin | 25 mg/m² i.v., days 1 and 8 | |
| Cyclophosphamide | 650 mg/m² i.v., days 1 and 8 | |
| Oncovin (vincristine) | 1.4 mg/m² i.v., days 1 and 8 | |
| Prednisone | 60 mg/m² p.o., days 15 and 29 | |
| | (repeat monthly) | |
| **ProMace-MOPP** | | Ref. [34] |
| Cyclophosphamide | 650 mg/m² | |
| Adriamycin | 25 mg/m² i.v., days 1 and 8 | |
| VP-16 | 120 mg/m² | |
| Prednisone | 60 mg/m² orally, days 1–14 | |
| MTX | 1.5 g/m² + leucovorin i.v., day 14 | |
| **M-BACOD** | | Ref. [33] |
| Bleomycin | 4 mg/m² | |
| Adriamycin | 45 mg/m² | |
| Cyclophosphamide | 600 mg/m² i.v., 3 weeks | |
| Vincristine | 1 mg/m² | |
| MTX | 3 g/m² | |
| | + leucovorin i.v. every 3 weeks, cycled inbetween | |
| **COP-Blam** | | Ref. [30] |
| Cyclophosphamide | 400 mg/m² | |
| Vincristine | 1 mg/m² day 1, i.v., 21 days | |
| Doxorubicin | 40 mg/m² | |
| Prednisone | 40 mg/m² orally, days 1–10 | |
| Procarbazine | 100 mg/m² | |
| Bleomycin | 15 mg i.v., day 14 | |

(b) The strategic option is more controversial in nodular mixed lymphoma (NML), which comprises approximately 15% of all NHL. A randomized trial showed no significant differences between NML and NLPD [15]. However, in a group of 31 patients with NML treated with C-MOPP the complete remission rate was 77%. More than 3/4 of the complete responders (79%) remained in remission at 5 yr [16], which is distinctly longer than the 2–3 yr remission duration reported in most other trials. On the other hand, the Eastern Cooperative Oncology Group (ECOG) did not find any difference in response rate or survival in a recent prospective study of patients treated with cyclophosphamide and prednisone or more aggressive chemotherapies (C-MOPP, BCVP) [18, 19].

(c) Most authors agree that patients with the nodular histiocytic (NH) form should be treated with aggressive combination chemotherapy designed to achieve complete remission [16, 20].

For unfavourable NHL there is nowadays general agreement that patients should be treated with aggressive combination chemotherapy. Early results with single agents or with the combination CVP have been disappointing [21, 22].

## MODERN COMBINATION CHEMOTHERAPY

A first improvement in the prognosis for aggressive NHL came with the introduction of C-MOPP [23] and several adriamycin-containing regimens [21, 24], mainly when the drugs were employed in a continuous, weekly manner similar to that used in the treatment of acute lymphoblastic leukemia [25].

An inadequate initial tumour reduction and/or a rapid tumour proliferation between chemotherapy courses were soon recognized as factors predisposing to induction failure or to early relapse. The development of central nervous system (CNS) disease in patients with lymphoblastic or 'large cell' lymphomas, particularly if bone marrow or retroperitoneal lymph nodes were involved, became increasingly frequent [26]. This complication is very distressing, since eradication of an established CNS disease in NHL is exceedingly rare.

Other parameters were found to have prognostic significance: immunologic markers, tumour bulkiness, serum LDH level, gastrointestinal tract involvement, anatomic stage and the presence of systemic symptoms [27]. However, most of these prognostic variables lose their importance as soon as a pathologically restaged CR can be demonstrated [16, 27, 28]. Different criteria used in restaging patients may therefore account for pronounced differences in survival among series with similar response rates.

A carefully restaged CR has been shown to be crucial for long-term survival of patients with NHL of unfavourable histology. About 60% of the patients achieving CR do not relapse, despite absence of maintenance chemotherapy, thus permitting the cautions attribution of the term 'cure' [6, 29, 30] (Table 1). A recent study underlines the importance of achieving CR with the primary treatment rather than relying on salvage therapy [31].

In recent years more intensive chemotherapy regimens have been devised, generally by eliminating or shortening therapy-free intervals and using drugs active on localizations in the CNS disease (Tables 1 and 2). The most successful programs use weekly cytoxan, adriamycin, vincristine and daily prednisone as initial cytoreductive treatment. Because of its pronounced antitumour activity in NHL [35], the podophyllotoxin derivative VP16/213 has been added to these agents [34]. Bleomycin (sometimes with vincristine) was often added during bone marrow recovery in order to decrease the prospects of relapse, while myelosuppressive cytotoxic drugs had to be omitted [32]. Methotrexate (MTX) and cytosine-arabinoside (ara-C) have been employed more recently in NHL [29, 33]. These two drugs as well as procarbazine penetrate the blood–brain barrier and may provide protection to the central nervous system.

As shown in Table 2, with these newer regimens of combination chemotherapy CR was achieved in 70% of the patients and the median actuarial survival was clearly prolonged compared to historical data. None of these patients groups have, however, been followed long enough to permit a definite assessment. Moreover, a prospective, randomized comparison between CHOP (Table 2) and one of the newer regimens has yet to be carried out. Such a trial is indicated because of the toxicity of the new treatments, ranging from severe myelosuppression to septic death in 3–10% of the cases [33, 34].

Several studies using MTX at high or medium doses, ara-C and more recently procarbazine report a decreased incidence of CNS disease [29, 30, 33, 34, 36]. However, all the trials with the combinations COMLA, ProMace-MOPP, M-BACOD and COP-Blam (Table 2) encompass too few patients with bone marrow involvement. Therefore an effective prevention of this complication has yet to be conclusively shown: furthermore, it is possible that this goal can be achieved only with a more aggressive approach, including, perhaps, cranial irradiation. It must in fact be remembered that a study carried out in

children with ALL suggests that cranial irradiation should remain a component of prophylactic CNS therapy and cannot be replaced by an intermediate dose of MTX (500 mg/m$^2$) [27]. Shapiro demonstrated that an MTX infusion of 500 mg/m$^2$ over 24 hr elicits, at best, a level of $6 \times 10^{-7}$ M in the cerebrospinal fluid (CSF) [38]. Freeman obtained a concentration of $10^{-5}$ M of MTX in the CSF over a longer time by the simultaneous administration of an MTX infusion (500 mg/m$^2$) with MTX intrathecally [39]. A concentration of $10^{-5}$ M MTX seems to be needed for a therapeutic effect on human cancer cells [40].

In conclusion, we feel that prospective randomized trials alone will be able to properly evaluate the newer regimens of combination chemotherapy (Table 1 and 2). Such trials could, however, still be somewhat premature, since the dosage and scheduling of certain drugs (particularly VP16 and bleomycin) in the newer regimens are suboptimal, whereas additional data are necessary to optimize the use of other agents like MTX and ara-C.

## SALVAGE TREATMENTS

In recent years the results of salvage treatment for aggressive lymphomas have been uniformily poor in patients whose disease has progressed after treatment by adriamycin-containing combinations. Only recently have there been encouraging preliminary reports of new effective salvage regimens.

Development of effective salvage treatment is not only medically important, since 20–30% of patients fail to achieve a complete remission with first-line chemotherapy. In addition, 20–40% of patients who have a CR will eventually relapse. These patients are uniformly destined to die, usually within 3–7 months, unless they achieve another CR with subsequent therapy. Moreover, the design of an effective second-line treatment could be used to improve the first-line therapy by alternating these effective regimens [16]. For the time being such a strategy cannot even be properly evaluated in NHL, since we lack second-line treatments of established efficacy. ProMace/MOPP can, however, be viewed as a first and partial step in this direction.

Encouraging results observed in salvage regimens with the use of bleomycin [41] and even vincristine [42] in continuous infusion have already led to an improvement of a front-line treatment in NHL [30]. Application of cytotoxic drugs by continuous infusion may augment the tumoricidal effect of a drug, by maintaining an adequate drug level for a longer time and affecting cells vulnerable only in certain phases of their cell cycle. In addition, side-effects are frequently less bothersome than after bolus injections. Ara-C and bleomycin are well-known examples of greater effectiveness if applied by continuous infusion.

Other authors have utilized the incorporation of new drugs in salvage regimens. Interesting results were obtained with a combination of iphosphamide, methotrexate and vincristine. The overall response and CR rates were 47 and 17% respectively, with 2/5 CRs being free of disease for more than 2 yr [43]. In a subsequent study VP16 was substituted for vincristine. Overall response and CR rates of 62 and 35% was obtained with the new regimen (IMVP-16) and represented a considerable improvement over those previously found [44].

Somewhat similar results were lately registered by the Swiss Group for Clinical Cancer Research (SAKK) with a combination of iphosphamide, vincristine and prednisone (10/17 PRs) [Kroner, personal communication]. The same group is now piloting a combination of DDP/VP16/bleomycin (the latter in continuous infusion) after having seen encouraging results with a combination of DDP/VP16 (5/13 PRs) in patients who were in most instances pretreated with an adriamycin-containing combination [45]. In the past the SAKK had already pioneered the introduction of the podophyllotoxines in salvage regimens by using a combination of adriamycin/bleomycin/VM-26 [46]. The role of VM-26 in these regimens remains somewhat uncertain: though recently combinations of this podophyllotoxin-derivative with either methyl-GAG or DDP and hexamethylmelamine have shown disappointing results [47, 48].

Important prognostic variables with respect to salvage treatment are slowly emerging. In the already mentioned report on IMVP-16, the authors were able to demonstrate that the quality as well as the duration of the response to second-line treatment could be correlated with the outcome observed with first-line therapy. Another observation was that the highest CR rate was seen in 5 patients who were partial responders to front-line treatment but were not improving any further. These patients were subsequently shifted to IMVP-16 before progressive disease was allowed to develop. This interesting observation as well as other prognostic factors may be important in analysing the results of salvage chemotherapy regimens. They might help to explain inconsistencies which might arise, as has been the case with ABVD in Hodgkin's disease [49].

Bone marrow (BM) transplantation represents another possible salvage treatment. A transplantation between identical twins for dis-

seminated NHL in patients who failed conventional chemotherapy showed a complete remission in 7 of 8 patients. Four of these patients remained in CR for 12–126 months [50]. Thus, intensive chemoradiotherapy and marrow transplantation can induce enduring remissions in NHL patients. Autologous BM transplantation after high-dose chemotherapy in patients with NHL resistant to conventional treatment has also been studied [51]. Cryopreserved autologous marrow was able to reconstitute marrow function following marrow-lethal cytoreductive therapy. Treatment failures in lymphoproliferative disease may, however, be caused by tumour cell contamination of the infused autologous marrow. Purging methods for residual tumour cells by immunologic or pharmacologic agents are currently being studied. It can therefore be speculated that in the future, BM-transplantation will not only represent a sophisticated salvage treatment, but could possibly be viewed as a component of the front-line therapy, as is already the case for heterologous BM-transplantation in young patients with AML and ALL.

## NEW DRUGS

Among the drugs which have entered clinical practice in the last years, only methyl-GAG, DDP and particularly VP16 have consistently shown antitumour activity in advanced lymphomas [35, 52, 53]. The experience at the M.D. Anderson with IMVP-16 and a randomized study performed in Australia (CVP vs a similar combination with VP16 replacing vincristine) have shown that VP16 is at least as effective as the vinca alcaloids [54].

The role of *m*-AMSA in the treatment of lymphoproliferative disorders remains somewhat unclear. After initial promising results with 3 CRs and 3 PRs out of 17 patients [55], later studies have been somewhat disappointing [Bramwell, personal communication; Coleman, personal communication]. These inconsistent results are probably related to patient selection, since this exquisitely myelosuppressive drug may be difficult to evaluate in heavily pretreated patients with impaired bone-marrow function. This situation should be less troublesome for an assessment of the antitumour activity of interferon. A confirmation of early results with leukocyte interferon [56] is still lacking. Some responses were reported in 3 multiple-dose phase I studies of recombinant leukocyte A interferon, a genetically engineered human leukocyte interferon.* These results are, however, very preliminary and must also be viewed within the context of several prognostic factors, e.g. the occurrence of spontaneous regressions in 10–15% of nodular lymphomas [57].

Interesting facts, which may be of therapeutic importance in the future, have been reported recently. Analysis of enzymes in lymphocytes revealed distinct patterns of activities, suggesting, for instance, that adenosine deaminase (ADA) is required for the maturation of thymic T lymphocytes [58]. Absence of ADA is thought to disturb the deoxynucleoside metabolism, thereby impairing cell growth and survival *in vitro*. The specific ADA inhibitor 2′-deoxycoformycin did indeed have a favourable effect in T cell diseases [59]. Unfortunately, responses have so far been only short lived. Moreover this compound elicited an unacceptable degree of toxicity [60]. Using a lower dosage (5 mg/m$^2$ daily for 3 days, once every 3 weeks), the ECOG is currently comparing this agent to the non-myelosuppressive drug spirogermanium, which looks promising [61]. A phase II study in advanced lymphomas with this latter compound has recently been activated also by the Early Clinical Trials Group of the European Organisation for Research and Treatment of Cancer (EORTC).

## TREATMENT WITH COMBINED MODALITIES

The extent of disease at diagnosis has historically been a determinant for initial therapy. Patients with localized disease have generally been treated with radiotherapy; patients with extensive disease have received chemotherapy.

Several features of 'large cell' lymphomas have, however, recently led us to consider this context. Unfavourable NHL represents a tumour type which tends to have a high growth fraction [12]. A rapid spread via lymphatics or a haematogenous dissemination is frequently observed. In some series new manifestations of disease developed before radiotherapy was completed [62]. As could have been anticipated, better results have been obtained with radiotherapy in pathologically (= surgically) staged stage I disease [63] compared to results achieved in clinically staged limited disease [64].

Adjuvant chemotherapy appears to be a realistic therapeutic option in these stages. In two prospective randomized studies patients receiving additional chemotherapy after regional irradiation for stage I–II (pathologic staging in 98%) showed an improved and disease-free survival at 5 yr compared to radiotherapy alone, at least in unfavourable NHL [62, 65]. However, systemic

*Summary of phase I multiple-dose studies presented at the 13th International Cancer Congress, September, 1982, Seattle.

chemotherapy alone for stage I and II seems to be equally effective, with acceptable toxicity, and may avoid surgical restaging procedures [66]. Also, salvage chemotherapy of radiotherapy failures appears to be less effective in NHL than in Hodgkin's disease [65].

Bulky tumours, stage II presentations and abdominal disease are considered unfavourable for radiotherapy alone and require additional chemotherapy [67]. Chemotherapy as the initial treatment possibly eliminates failures due to early dissemination. In this approach radiotherapy given as a consolidation to the sites of initial bulky disease may still have a role, which remains, however, to be exactly defined.

The combination of irradiation and chemotherapy could theoretically improve results also in advanced diffuse NHL [68]. A significant proportion of patients in apparent complete clinical remission in fact have residual disease at completion of chemotherapy if surgically restaged [68]. Moreover, occult residual lesions are found in sites originally known to have been involved, and the pattern of relapse is mostly linked to the regions initially presenting with bulky disease [16]. However, all randomized trials evaluating this combined approach in advanced NHL have so far been hampered by different kinds of increased toxicity. Therefore the optimal way of combining both modalities also remains to be defined here.

## NHL WITH SPECIAL FEATURES

Besides NHL with a gastrointestinal tract involvement as initial or late manifestation, which presents peculiar therapeutic problems [69], there are other subtypes of particular interest.

Lymphoblastic lymphoma, a recently defined subgroup of diffuse NHL, occurs in adolescent males [70]. Patients present mostly with a mediastinal mass. Bone-marrow involvement is frequent and there is a tendency for early leptomeningeal manifestations. Median survival is shorter than for other subtypes of NHL. Several reports suggest that aggressive treatments incorporating concepts used in the therapy of acute leukemias may improve long-term survival [71, 72]. Most authors include some form of CNS prophylaxis. Differences in important clinical parameters were found between children and adults [70], which may lead to different therapeutic approaches in the two age groups.

In recent years attention has been given to function and heterogeneity of T cells in haematological disease. Apart from the above-mentioned lymphoblastic lymphoma, the syndrome of adult T cell lymphoma–leukemia has recently been identified [73]. Patients with this disease were mostly of Japanese or West Indian Caribbean origin. Clinically, the disease is characterized by a rapidly progressing lymphoma in adults with early blood and bone-marrow involvement. The most striking additional feature is hypercalcemia, which seems to be related to the activity of the disease. The disease is possibly caused by an RNA leukemia virus, the so-called human T cell leukemia–lymphoma virus (HTLV), which was isolated from fresh peripheral cells [74].

Mycosis fungoides and Sezary syndrome belong to the so-called cutaneous T cell lymphomas (CTCL). Their treatment for different stages has recently been reviewed [75] and favourable response to chemotherapy or monoclonal antibodies was reported [76]. CTCL remains, however, a somewhat ill-defined group of diseases and further clarification is urgently needed. This is important, since old epidemiologic data are probably misleading. In fact, with increased awareness and earlier diagnosis, it appears that CTCL has an incidence at least equal to that of Hodgkin's disease [77].

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