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Advances in lymphoma treatment

L M LEVY, M SONQISHE

SUMMARY

There have been considerable advances in the management of patients with lymphoma over the past three decades. In Hodgkin's disease, there was a major break-through in the late 1960s with the development of the MOPP combination regimen.

Using this and other more recent combinations, remission rates of up to 80 pc may be achieved overall with many patients having durable remissions. In non-Hodgkin's lymphoma there have been few advances in therapy of the indolent low-grade varieties which remain largely incurbable. In the aggressive high-grade lymphomas, some subtypes have proved highly responsive to intensive cytotoxic programmes, giving remission rates and relapse-free survival rates of 70–80 pc. Certain categories, however, such as lymphoblastic lymphoma, remain a problem. Bone marrow transplantation and biological response modifiers have been important recent developments. The search for treatment strategies that improve survival and have relatively low toxicity is a continuing challenge.

Abbreviations: CT = Chemotherapy, RT = Radiotherapy, TBI = Total body irradiation, ABMT = Autologous bone marrow transplantation, BMT = Bone marrow transplantation, BRM = Biological response modifiers, NHL = Non Hodgkin's lymphoma and HD = Hodgkin's disease.

INTRODUCTION

The field of lymphoma therapy has proved to be one of the most rapidly developing areas in medicine. During the past two to three decades, greater understanding of the histological patterns and disease processes has led to important advances in tumour definition, staging and therapeutic approaches. Scientists have collaborated closely with clinicians in defining the mode of action and adverse effects of cytotoxic agents, and well-structured clinical trials have been performed. The introduction of oncology centres which utilise the services of many experts from different specialities in a co-ordinated manner has also contributed to the improved results seen today. Several different treatment modalities are now available, including surgery, radiotherapy, chemotherapy, bone marrow transplantation and biological and immunological approaches. The progress achieved has led to the despondency of the past being replaced by optimism. Advances in lymphoma treatment are reviewed in this paper.

HODGKIN'S DISEASE: Radiotherapy was the earliest form of lymphoma treatment.[1] Widefield techniques with irradiation of multiple node chains were introduced and tumoricidal dose levels identified.[2] For many years, radiotherapy was the only effective treatment modality, Nitrogen mustard, the first cytotoxic drug, was used for HD in the 1940s with little success.[3] As other drugs became available e.g. cyclophosphamide and vincristine, they were used as single agents to treat HD, with results little better than in untreated patients.[4] The design of early drug combinations was based on considerations of pharmacological action and tumour cell kinetics. The major breakthrough came with the development of the MOPP regimen (mustine, oncovin, procarbazine and prednisolone).[5] This combination led to a number of lasting remissions in patients with advanced disease. Thus in the 1960s with improvements in radiotherapy and the advent of MOPP, the possibility of cure for Hodgkin's disease was raised for the first time.

Since then many more reports have confirmed the efficacy of MOPP which produces remission rates of up to 80 pc in patients with advanced stage disease.[4,6] But although the initial remission rate is high, a number of patients relapse. The proportions vary from 14–50 pc in different studies.[7,8] In addition, with improved survival a number of complications became evident, the most important being growth retardation, infertility and second malignancies.[9]

Because of this, many complementary or alternative chemotherapy approaches have been investigated, including extending the duration of treatment, the addition or substitution of drugs such as chlorambucil, adriamycin and the nitrosources, alternating sequences of non-cross-resistant agents or supplementing chemotherapy with irradiation. None of the MOPP-modified regimens have yielded improved results, but the introduction of non-cross-resistant programmes such as ABVD (adriamycin, bleomycin, vinblastine, dacarbazine) appears to improve survival with fewer side effects.[8]

For many years, combined modality treatment has been used in all stages of HD. The current trend is in the direction of employing lower doses of irradiation. Encouraging results are reported by some[10] but not others.[11]

The standard treatment approach today for Stage I and II disease is radiation therapy alone, i.e. 'mantle' or 'inverted Y' fields.[12] Good results with relapse-free survival rates of 75–90 pc have been

obtained,[13] but there is a high incidence of recurrence. For this reason, some oncologists are now advocating the use of cytotoxics for all stages,[14] an approach first used in Uganda.[15]

The optimal management of State IIIA is still debated. Relapse-free survival with radiotherapy alone is lower than with Stage I and II disease.[13,16] For Stage IIIB and IV disease, chemotherapy is the treatment of choice. The largest experience has been with MOPP but alternating non-cross-resistant programmes provide a rational alternative and may prove superior.

Over the years, the concept of dose intensity (total equivalent dose) when devising new cytotoxic regimens has received much attention. The combination of active drugs with non-overlapping toxicity is sound strategy, as drug doses can often be increased sufficiently to overcome drug resistance of the tumour without significant adverse effects. This concept has made possible many of the successes of combination CT both in HD and NHL. Methods of identifying the optimum combination of active drugs have been devised, reducing the number of clinical trials that would otherwise be needed.[17]

In spite of this, toxicity, particularly myelosuppression, is often a limiting factor. Because of this the role of bone marrow transplantation has become important in recent years, as it allows the administration of cytoreductive therapy with curative intent without regard to lethal marrow effects. Results from the largest published series of ABMT in patients with HD show that about half (43–48 pc) of patients not responding to primary induction therapy obtained complete remission, and in 24–34 pc these remissions were maintained.[18] Toxicity and morbidity are, however, high (death rate 10 pc).

It is not clear which patients would benefit most from this procedure, as the patients studied to date are mainly those who do not obtain a remission with CT, or who relapse early or repeatedly. Earlier transplants in high risk patients may improve survival. Suggestions of means of identifying such patients include elevated ESR or serum alkaline phosphatase, anaemia or unfavourable histology.

Questions still remain about the most effective conditioning programme (CBV-cyclophosphamide, BCNU and etoposide is currently the most popular) and whether dose escalations or addition of radiotherapy would improve results or just increase toxicity. Most work has been done on autologous BMT which carries no risk of graft-versus-host disease. Allogenic marrow, however, has the possible advantage of a grant-versus-Hodgkin's disease effect and no risk of reinfusing tumour cells. Most workers favour autologous BMT but the issue of 'purging' the marrow of tumour cells using immunological or pharmacological methods is another controversial area.

A new and totally different approach is that of biological response mediators. This is discussed later.

In the past 25 years, disease-free survival for advanced Hodgkin's disease has risen from zero to over 60 pc.[19] The question is no longer whether cure is possible but how it may best be achieved.

NON-HODGKIN'S LYMPHOMA: The first effective form of therapy identified for non-Hodgkin's lymphoma was irradiation, but less than 10 pc of all patients were rendered permanently free of disease.[20] Although progress has parallelled the advances in Hodgkin's disease, the evolution in treatment strategy is more difficult to document because of the differing clinical features and natural history of the various subtypes.

High and intermediate grade non-Hodgkin's lymphoma: Following the success in HD, combination therapy was applied to NHL but with less satisfactory results. In 1975, De Vita and co-workers published the first report of disease-free survival in a fraction of patients with advanced diffuse high grade lymphoma using combination CT (MOPP or MOPP plus cyclophosphamide).[21] These and various similar combinations gave complete remission rates of 20–60 pc,[22] but results were inferior in clinically aggressive sub-groups with diffuse histology.

During the 1970s, the activity of adriamycin was established and this is the most effective agent to date for high grades of NHL. Various combinations incorporating this drug such as CHOP (cyclophosphamide, adriamycin, oncovin and prednisolone) and BACOP or CHOP-Bleo (CHOP + bleomycin) have led to complete remission rates of 40–70 pc in patients with extensive disease, with approximately half of the responders remaining disease-free for several years.[22,23]

More intensive regimens were then developed, such as M-BACOD (methotraxate, bleomycin, doxorubicin, cyclophosphamide, vincristine, dexamethazone), A-COMLA (adriamycin,

cyclophosphamide, vincristine, methotrexate, leucovorin and cytarabine) and many other complex combinations. These have produced complete remission rates 55–84 pc and greater than 75 pc relapse-free survivals.[24] These intensive programmes exhibit considerable toxicity and it has not been clearly documented that CHOP, delivered in full dosage, is inferior. Several newer chemotherapy agents are currently being evaluated, including etoposide, cis-platinum, pyrazofurin, vindesine, M-AMSA and clorozotocin.[25,26] The evolution of new chemotherapy concepts has results in new chemotherapeutic approaches, which still require clinical confirmation.

Certain subsets of aggressive NHL, such as lymphoblastic and Burkitt's, have a poor prognosis if treated with conventional programmes, the reasons being are that they exhibit a high nervous system recurrence rate and also rapidly become refractory to chemotherapy. Thus central nervous system prophylaxis is important, plus use of multiple agents to prevent emergence of a resistant clone of cells. Many workers feel that lymphoblastic lymphoma is best treated as ALL. In Burkitt's lymphoma, combinations of cyclophosphamide, vincristine, cytosine arabinoside and methotrexate[27,28] have produced longer remissions than cyclophosphamide alone. The use of adriamycin may improve results.[29]

The role of radiotherapy in the treatment of high and intermediate non-Hodgkin's lymphoma is less well-defined than in Hodgkin's disease, but the results are considerably poorer in Stage II than Stage I.[22] True Stage I disease is rare. In addition, relapse occurs commonly. With more extensive disease, radiotherapy is seldom adequate to eradicate disease.

The value of combined modality treatment is not clear. Radiotherapy in various forms has been combined with cytotoxic combinations with promising results in early stage disease.[23] A report in which patients with advanced stage NHL were treated with CHOP and total body irradiation suggests a possible advantage for combined modality therapy.[30]

Current recommendations therefore are that RT may be successful in patients with localised areas of involvement, but for all stages beyond this cytotoxics are required. The recognition that CT can produce long term relapse-free survival in patients with advanced disease has prompted its use in all stages. The natural history of these aggressive lymphomas is so poor whatever the chosen therapy, it is important to treat early and maximally. The goal is complete remission, as only these patients demonstrate prolonged survival and potential for cure.

Despite the uncertainty about the best regimen, certain principles in the treatment of high grade NHL have been established. For a regimen to be curative in a substantial number of patients, it must achieve a high rate of complete remission with frontline therapy, and drugs should be delivered at maximum dose intensity. Prolonged treatment is not necessary.[25] Although there is a high rate of early relapse, there are few relapses beyond two years. The dose intensity can now be augmented by using recombinant growth factors, which reduce the severity and duration of treatment-induced leucopenia.[26]

Thus over the past two decades, improved aggressive combination chemotherapy regimens for advanced intermediate and high grade NHL have resulted in greatly improved complete remission and cure rates. In a significant number of patients, however, the disease is refractory to initial therapy or relapse occurs. Such patients have a particularly poor prognosis. Recent studies suggest that high dose CT and/or RT plus BMT are effective.[31] As with HD, the dose limiting toxicity with CT's myelosuppression, thus BMT has come to play an important role as salvage therapy. Long term disease-free survival after BMT ranges from 20–50 pc in different studies.[32]

The status of the tumour at the time of transplantation is important. Patients transplanted early in the course of disease do much better than those having drug-resistant relapses (three years disease-free survival < 10 pc),[32] or who have been heavily pretreated.[31] Several groups have evaluated the role of high dose CT plus ABMT given during first remission as consolidation or intensification in patients believed to be at high risk for relapse. Although patient numbers are small and several histological types are included, the overall complete remission rate is approximately 66–70 pc and several patients have survived more than two years and are still disease-free.[31,33]

Because of the excellent early results, bone marrow transplantation should no longer be used as salvage therapy only in NHL but should be considered at an early stage (ie first remission) in

patients with poor prognostic features (e.g. adverse histology, high bulk disease, high lactic dehydrogenase, anaemia).

LOW GRADE NON-HODGKIN'S LYMPHOMA: The low grade lymphomas are usually indolent clinically and of advanced stage at diagnosis. They are highly responsive to a variety of treatments.

For Stage I and II disease regional field and total lymphoid irradiation, combined RT and CT, and CT alone have been used.[34] Studies are limited because of the rarity of this presentation, but long term disease-free survival may be achieved particularly in patients below 40 years of age.[33]

In most patients, involvement is widespread at presentation. The management of Stage III and IV disease is controversial because standard approaches have not proved curative despite high remission rates. Significant advantages of various regimens have been difficult to prove because of the lengthy observation needed, small patient numbers and toxicity of intensive therapy in older patients.

Some trials of single alkylating agent (usually chlorambucil), combined CT, TBI or both CT and RT have shown no significant difference in complete remission rates (65–83 pc), relapse-free survival (50 months median) or overall survival (60+ months).[34,35,36] Other studies, however, have shown better relapse-free survival with combination CT though remission rates and median survival are similar.[37] There appears to be little correlation between dose intensity and remission though relapse-free survival improves as dose intensity increases. Fludarabine is a promising new drug currently under evaluation.

In 1979, Portlock and Rosenberg suggested no specific therapy for indolent low grade lymphoma until dictated by symptoms.[38] They found that ultimate survival was not significantly different from that of comparable patients treated more intensively. Later studies, however, tend to support prompt treatment at diagnosis.[39] Whatever treatment is used, the disease-free survival curves demonstrate a constant risk of relapse at a rate of 10–15 pc per year.[36] Adverse prognostic features include degree of nodularity, presence of B symptoms, bulk disease, elevated serum lactic dehydrogenase and anaemia.

As more sensitive molecular methods have been developed, it has been shown that most patients in complete remission have circulating monoclonal B lymphocytes present. These cells may explain the continuous late relapses seen in advanced low grade NHL, and may prove useful as a prognostic indicator.[36]

An important biological feature of low grade lymphomas is the emergence of an aggressive histological subtype with a short survival time. ABMT has been studied in these patients but the prognosis is still poor.

There is little data available regarding ABMT in low grade histologies.

New approaches and future trends: Over the past two to three decades, great therapeutic advances have been made using combined CT, RT and BMT. Some results are excellent but there are still patients treated who can neither be cured nor benefit from prolonged survival times. In addition, patients have an increased risk of developing second malignancies or myelodysplastic syndromes. There was thus a need to develop new therapeutic concepts and much attention recently has been directed towards the fields of immunology and biological response modifiers.

The work began with primitive immunostimulants but now encompasses a spectrum of agents including interferons, interleukin 2, tumour necrosis factor, lymphokine activated killer cells, haemotopoietic growth factors and monoclonal antibodies.

Most cytokines act principally through their effects on the immune system, enabling some patients to mount an effective anti-tumour response. Some have a synergistic effect when used with cytotoxic agents, some have anti-tumour activity, and the growth factors lead to accelerated recovery from myelosuppression.[40,41]

Of the cytokines, the interferons have been most fully studied, and in the lymphomas some interesting results have been obtained. Objective response rates to alpha-interferon of 40–50 pc have been documented in low grade NHL. Responses are partial with median duration of 6–12 months, and are not significantly influenced by histology, stage, or prior treatment. The lower response rate of 10–15 pc for aggressive NHL and HD has been discouraging.[42,43,44,45] Combinations of interferons and cytotoxics appear more promising, but toxicity is a problem.

Interleukin-2 has been used only minimally in the treatment of NHL to date, but early results are encouraging.

Studies have been performed with monoclonal antibodies, but their use has been limited by technical difficulties and the results are variable.[44] In general, responses have been partial and transient but dramatic improvement has been recorded in occasional cases. In all fields of biotherapy better results are obtained when the tumour load is low and the immune system not compromised.

Immunisation with tumour antigen to prevent relapses and/or prolong survival is another interesting concept which may be developed further.[44]

While these complex biological approaches are still experimental and have as yet led to cure in only small numbers of patients, it appears they may have a role to play in the future.

CONCLUSIONS

With these developments in treatment, many patients with HD are now curable. In NHL a paradox has become evident. The 'favourable' prognostic groups (low-grade NHL) — so-called because of indolent natural history and slow progression — are with few exceptions incurable by current methods. Conversely, with 'unfavourable' or high-grade histology, a considerable proportion of complete responders remain free of disease. With this latter group, initial selection of an appropriate treatment is essential as the possibility of achieving cure is notable inferior in previously treated patients. Bone marrow transplantation has been an exciting development and has a definite role to play in carefully selected patients.

These advances mean that many patients with lymphomas that were previously universally fatal can either be cured or have substantial palliation. In some groups, however, the survival results are still unsatisfactory and several controversial issues remain. The optimal therapeutic strategy for many patients is uncertain.

The value of other technique in treatment such as biological response modifiers, monoclonal antibodies and other forms of immunotherapy will, hopefully, soon become clearer. The definition and value of prognostic determinants is becoming increasingly important and may greatly influence selection and outcome.

As superior treatment programmes improve survival rates in all the lymphomas, further vital issues arise, such as the long-term cumulative drug effects on tissues and the sequelae from mutagenic and carcinogenic agents. The development of programmes that improve both survival and safety is an on-going challenge.

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