Review Article

Large-cell lymphocytic lymphoma

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Summary

Progress in the treatment of large-cell lymphocytic lymphoma during the last decade has been such that cure has replaced palliation as the objective of treatment. In pathologically proven stage I or II disease appropriate radiotherapy is adequate.

It is of major importance to recognize that even in stage III or IV disease cure is possible, and it is therefore in the patient's best interests that initial assessment take into account the morphological and immunobiological features of the tumour as well as other prognostic factors, and that a chemotherapeutic regimen of established efficacy be prescribed.

Newer challenges are a need to define optimum chemotherapy and explore the roles of bone marrow transplantation and immunological manipulation of the tumour with monoclonal antibodies.

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The clinical course in the patient with a biopsy-proven diagnosis of lymphoma may follow one of two distinct courses. Either progression will be slow, with survival measured in years, and in the majority of cases the tumour cell will be a small round or cleaved lymphocyte and the nodal architecture will be follicular (the indolent group), or the neoplasm will grow rapidly and will be of high bulk, survival will be measured in months, and the tumour cells will be large and the node diffusely effaced (the aggressive tumours). The latter group is of interest because during the last decade anthracycline-containing chemotherapeutic regimens have changed the outlook to the extent that cure rather than palliation is the clear objective of current management.

Survival is determined by three related variables — the histopathological features of the tumour, host prognostic factors, and the chemotherapeutic agents used.

Histopathological features

For a long time the aggressive tumours, the distinctive feature of which was median survival between 3 and 6 months, were called reticulum cell sarcomas.[1] The name of these high-grade lesions was changed to histiocytic lymphoma on the basis that the microscopic features of the tumour cell most closely approximated that of the normal histiocyte.[2] It has subsequently become clear that while true histiocytic lymphomas may occur,

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these are a heterogeneous group of disorders[3] in which the majority of the cells are transformed B lymphocytes. Consensus has recently been reached on how the tumours should be classified, and it is important that each morphologically distinct entity be identified accurately.[4] Undoubtedly this is a step in the right direction, but it will be some years before sufficient information is available to assess the applicability of this international grouping of the lymphomas objectively, and even longer before its routine use becomes the basis for reporting results in clinical trials. Nevertheless, there is no reason to persist with older and more personal approaches except, perhaps, by including the latter in brackets after the approved terminology.

While endorsing universal acceptance of the recently introduced international classification, it is necessary to recognize that it does not adequately take into account rapid advances occurring in the understanding of lymphocyte immunobiology. Morphologists have concentrated on superficial similarities between tumour cells and those occurring in normal lymphocyte development without including measurements of enzymes, such as terminal deoxynucleotidyl transferase, and cell membrane surface markers in accurately defining the neoplastic population. Even this does not go far enough, since the presence of a particular clone identified with an antibody provides no information about cellular function. Such inertia, while comforting to the histologist, is hardly likely to contribute in any major way towards understanding the histogenesis of the lymphomas. It would therefore seem desirable to encourage the more widespread use of an immunohaematological approach, including examination of suitably prepared imprints and monoclonal marker studies carried out on cell suspensions. Failure to incorporate all of the currently available diagnostic information severely limits the value of any report, and may compromise the entry of patients into clinical trials and hinder the subsequent evaluation of response to specific chemotherapeutic regimens.

In addition to the need to develop a more scientific approach to classification there is a need to see the place of staging procedures for patients with lymphoma in clearer perspective. There is little agreement on whether these should extend beyond computed tomography to include surgical exploration. Nevertheless, until this dilemma is clearly resolved students of lymphoma need to have a clearly defined policy regarding these important decisions. It is necessary not only to take into account the correct sequence of the investigations when the patient is first seen but the increasingly important question of restaging to confirm complete remission. Indeed, abdominal or thoracic surgery may have its most decisive role in obtaining tissue for histological study to reveal the subclinical persistence of occult disease. It is on such information that the survival of an individual may ultimately rest.

Prognostic factors

Concerning poor host prognostic factors, a number of clinical associations are recognized.[5,6] These include male sex, bone marrow involvement, the presence of high-bulk disease (particularly in association with gastro-intestinal tract involvement), invasion of the central nervous system, a falling haemoglobin concentration and a rise in lactic dehydrogenase values. It is unacceptable for any patient with aggressive lymphoma who is being considered for chemotherapy to be

entered into a treatment programme without due consideration being given to each of these variables. In the majority of cases the host factors exert their effect on survival by influencing the number of patients who achieve complete remission. For example, involvement of the bone marrow — stage IV rather than stage III disease — or the presence of high-bulk disease means that prognosis is poor, this having important bearing on the choice of therapeutic alternatives, including bone marrow storage for autograft 'rescue' following more aggressive treatment during which marrow destruction becomes rate-limiting.

Response to chemotherapy

In the final analysis it is the response to chemotherapy that has the greatest influence on survival, and it is inexcusable to speak of remission rates without defining their duration and the characteristics of survival curves for patients off chemotherapy.

In pathologically defined stage I or II disease cure is possible with appropriate extended-field radiotherapy.[7,8] A diffuse lymphocytic lymphoma of the large-cell variety is a high-grade neoplasm with a multicentric site of origin. Since there is a significant difference between radiotherapy for stage I disease and that for stage II, an alternative approach is to use clinical staging and chemotherapy only.[9] Until such time as these issues are resolved, there is much to recommend meticulous pathological staging followed by radiotherapy given with curative intent and supplemented by adjuvant chemotherapy.[10]

In stage III and IV disease single agents may result in dramatic response and even cure. However, this practice is unacceptable because the complete remission rate is statistically inferior to that in patients receiving drug regimens containing doxorubicin (adriamycin) or one of its analogues. The single most important advance in the treatment of these patients has been the development of regimens incorporating an anthracycline antibiotic, which have increased rates for both complete remission and long disease-free survival. Furthermore, the presence of a plateau on the survival curve of patients treated in this way has led to the recognition that cure is possible in patients with highly malignant lymphomas.[11] The drug regimens have become increasingly more aggressive and complex, exemplified by CHOP (cyclophosphamide, hydroxydaunorubicin or adriamycin, Oncovin (vincristine), and prednisone),[12] BACOP (bleomycin, adriamycin, cyclophosphamide, Oncovin, and prednisone),[13] and M-BACOD (methotrexate, bleomycin, adriamycin, cyclophosphamide, Oncovin, and dexamethazone).[14] Encouraging results have also been obtained with the antimetabolite-containing regimens MEV (methotrexate, Endoxan (cyclophosphamide), and vincristine)[15] and COMLA (cyclophosphamide, Oncovin, methotrexate, leucovorin (folic acid) rescue, and arabinosyl cytosine).[16]

Against all these advances must be weighed cumulative drug toxicity and the risk of developing secondary malignant lesions.[17] A recent study[18] has demonstrated that in previously untreated patients a combination of the epipodophyllotoxin VP-16-213 with doxorubicin has a similar complete remission rate to C-MOPP (cyclophosphamide, Oncovin, procarbazine and prednisone)[19] and BACOP.[13] However, while the median survival has not been reached for these studies and the 2-year actuarially predicted survival curves are not statistically different, observations at 5 years show that C-MOPP and BACOP are superior. It is not clear what the explanation for these differences is. They may be explained by variations in studies between institutions or a fundamental and therefore important response to the drug regimens themselves, and a prospective trial is now in progress to resolve this issue.

Conclusions

What should be concluded from these remarks?

A significant number of patients with stage III and IV large-cell lymphocytic lymphoma are curable. Since these aggressive

lymphomas are heterogeneous and results may vary between subgroups, it is imperative that histological terminology be standardized and that classification always include histochemical and immunological measurements. At presentation clinical staging may be acceptable with the advent of high-resolution techniques, but these are less useful in confirming complete remission, at which stage exploratory surgery with multiple-site biopsy may well have a major role to play. Modern chemotherapy requires at least two agents, one of which must be an anthracycline antibiotic.

These dramatic advances clearly illustrate the vital importance of carefully designed and meticulously executed clinical trials. Such painstaking research is only possible when a multidisciplinary approach brings together the special expertise of haematologists, oncologists, radiotherapists, pathologists and surgeons. It follows that with cure becoming a reality for many patients, their best interests will be served by early referral to a centre where such a practice is established.

And what of the future? Already there are new challenges to face. Which histological or immunological subsets predict success or failure in response to current therapeutic programmes?[20] Which of the host prognostic factors are most important, and are they interrelated? Does central nervous system invasion present special problems? What are the best criteria for defining completeness of remission? At what point is increasing chemotherapy offset by morbidity in both the short and the long term? Will further roles for bone marrow transplantation or immunological manipulation with monoclonal antibodies emerge?

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