Treatment of aggressive non-Hodgkin's lymphoma in adults - are we doing any better?

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Great improvement in the treatment of patients with aggressive non-Hodgkin's lymphoma (NHL) has been obtained with the introduction of new combination chemotherapy regimens in the 1970s. The hope that there would be further improvement has waned during recent years due to the fact that some controlled studies did not reveal any better results using the new more intensive treatment regimens. This is the reason for the question: are we doing any better?

INTRODUCTION

Among the aggressive NHL, this review will discuss large-cell NHLs because they constitute the majority of the aggressive NHLs and most clinicians treat these patients independently of the histological subtype. In the Kiel classification, the large-cell NHL includes the centroblastic, immunoblastic and anaplastic subtypes [1]. The lymphoblastic NHL is a distinct clinical entity and will not be included here. In the Working Formulation [2], which was originally a 'translation scheme' between different classifications, large-cell NHLs are found both within the high-grade and the intermediate-grade groups. In the most recent classification, the Revised European-American Lymphoma (REAL) classification [3], which is developed from the Kiel classification, the large-cell NHLs include the diffuse large B-cell and anaplastic large cell lymphomas of T and null cell type. Compared to the Working Formulation the REAL-classification seems to offer additional information of clinical value [4] and this classification will probably dominate in the future.

There are many different factors that are reported to predict the prognosis for patients with newly diagnosed large-cell NHL. Besides stage and age, the level of serum lactodehydrogenas (LD) has been the most useful prognostic factor. Together with performance status and the number of extra-nodal sites, these factors form the basis for the International Index [5] which identifies four risk groups in patients treated with an anthracyclin-including regimen. For younger patients (< 60 years) an age adjusted prognostic model has been proposed based on tumor stage, serum LD and performance status. The age adjusted International Index has been widely used recently although the level of serum LD alone might be superior for predicting prognosis [6]. The achievement of a complete remission (CR) is always a favourable prognostic sign but it becomes controversial if a rapid CR is taken as value [7].

LIMITED DISEASE

Of large-cell NHLs, 30% are localized at diagnosis (i.e. in clinical stage I or II according to the Ann Arbor classification). Certain extra-nodal sites such as localized disease in the central nervous system (CNS), in the testis and the gastrointestinal tract, have unique clinical features and will not be discussed here.

Radiotherapy alone gives an unacceptable high relapse rate in studies of both stage I and II patients. A large tumor [8], a high age [9,10] and an elevated level of serum LD [10] are factors
reported to increase the risk of relapse after radiotherapy alone. Most authors recommend a combined treatment policy [11-13] both for stage I and II patients with 3-4 courses of an anthracyclin-containing regimen, such as CHOP [14], followed by radiotherapy. However, analysing only stage I patients, approximately 60-70% of the patients can be cured using local radiotherapy alone [8,9]. Yahalom et al. [15] performed a small randomized trial comparing radiotherapy alone to radiotherapy followed by CHOP in 44 stage I patients. The result favoured the combined treatment. However, the disease-free survival among the patients treated with radiotherapy alone was very low, making the result of this study questionable. A larger study was performed by Aviés and coworkers [16] who randomized 316 patients (mainly large-cell NHL) in stage IA of Waldeyer’s ring between radiotherapy alone, radiotherapy followed by CHOP or a CHOP-like regimen and chemotherapy alone. The 5-year rate for failure-free survival was 48% for radiotherapy, 45% for patients treated with chemotherapy, and 83% for the combined therapy. Overall survival was also better in the combined therapy arm. In the study, 36% of the patients had bulky disease and 29% had multiple tumors in the Waldeyer’s ring indicating a bad prognosis using radiotherapy alone for many patients.

Chemotherapy alone seems to be inferior to the combined treatment as shown by Aviés et al. [16] and two other large randomized studies including both stage I and stage II patients [17,18]. In the study by Glick and coworkers [18], using eight courses of CHOP with and without radiotherapy, the disease-free survival was significantly longer for patients using the combined treatment. Overall survival was close to being significantly better for the combined group. In the study by Miller and coworkers, [17], the treatment consisted of eight courses of CHOP or three courses of CHOP followed by local radiotherapy. The overall survival significantly favoured the combined treatment but the disease-free survival was not significantly different. The survival difference was due to excess deaths (primarily cardiac arrest occurring after completion of treatment) in the eight courses of CHOP arm. One important difference between these two studies is that the former study [17], but not the latter [18], included patients with bulky disease. One interpretation is that radiotherapy is especially important for creating local control in patients with bulky disease.

In conclusion, a combined treatment of a brief course of chemotherapy followed by local radiotherapy is recommended for most patients with limited disease. In a subgroup of patients with stage I, small tumour and normal S-LD, it is not known whether the combined treatment is superior to radiotherapy alone and merits a randomized study.

**GENERALIZED DISEASE**

Chemotherapy is the standard treatment for patients with generalized disease (stage III-IV). The golden standard combination, CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) [14] gives a 60% CR rate. However, half of the patients obtaining CR will relapse and thus only about one-third of patients with generalized large-cell NHL are cured by the CHOP regimen [19].

Adjuvant radiotherapy has been reported to improve the results in patients with generalized disease especially when applied to sites of initial bulky disease [20-22]. However, other investigators have found no indication of adjuvant radiotherapy [23,24]. The only controlled study comes from Aviés and coworkers [22] who randomized 88 patients in CR with initially bulky disease between those who had received adjuvant radiotherapy or not. The disease-free survival was significantly better for the patients who had received radiotherapy. The value of consolidation radiotherapy is, however, controversial and it is important to evaluate in more controlled studies.

More intensive drug combinations than CHOP look promising in pilot studies. The interest has focused upon an increased number of cytotoxic agents (Goldie and Coldman hypothesis [25]) as well as increased dose intensity (more is better hypothesis). In most chemotherapy combinations, these two concepts have been mixed. During recent years, the use of haematopoetic growth factors has led to the development of new more intensive regimens. With the possibility of rescuing the patient using stem cells either collected from the bone-marrow (ABMT) or from peripheral blood (PBSC), very high doses of cytostatic drugs have become feasible to administer.

**PRIMARY TREATMENT WITH COMBINATIONS MORE INTENSIVE THAN CHOP-WITHOUT STEM CELL SUPPORT**

Retrospective studies evaluating the role of dose-intensity have shown conflicting results. In a French study using a combination including mainly cyclophosphamide, doxorubicin and vincristine, a high-dose intensity was found to be important for the outcome [26]. Another retrospective study by Kwak and coworkers [27] reported that a dose intensity for doxorubicin of >75% was the single most important predictor of survival for a subgroup of patients with good

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