Selected Summary

ACVBP Versus CHOP Plus Radiotherapy for Localized Aggressive Lymphoma

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SUMMARY

Non Hodgkins Lymphoma (NHL) is the commonest haematological malignancy.[1] During the past decade major progress has taken place in understanding the biology of NHL. For patients with aggressive lymphomas, initial chemotherapy using cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) remains the treatment of choice. Three year progression –free survival varies from 40% (for high risk patients) to 70% for low risk patients.[2] For early stage disease (low risk) involved field radiotherapy (IFRT) has been added to chemotherapy to reduce the relapse risk.[3-4] In order to improve the outcome further, various 2nd and 3rd generation chemotherapeutic regimen (multiple drugs at more frequent intervals) have been used but these were not found superior to CHOP chemotherapy.[2]

The Groupe d'Etude des Lymphomdes de l'Adulte (GELA) has developed a chemotherapy regimen that consists of an induction phase of intensified doxorubicin, cyclophosphamide, vindesine, bleomycin and prednisone (ACVBP) followed by sequential consolidation. In an earlier study with this chemotherapy regimens for intermediate or high-grade lymphoma the estimated five-year overall survival among patients with localized disease who received the ACVBP was 80%.[5]

The present randomized study was launched to compare the ACVBP regimen with chemoradiotherapy in patients under 61 years of age who had localized aggressive lymphoma and no adverse prognostic factors, as defined by the age adjusted International Prognostic Index.[6]

In this prospective multicentric randomized study,[7] a total of 647 patients were enrolled between March 1993 and June 2000 at 86 participating centers; 328 patients received chemotherapy alone with ACVBP and 329 were randomized to receive CHOP chemotherapy plus IFRT. Eligibility criteria were – age more than 15 years and younger than 61 years of age, newly diagnosed aggressive lymphoma (diffuse mixed, diffuse large cell or immunoblastic according to the working formulation and anaplastic according to the updated Kiel classification) and to have no adverse prognostic factors according to the age-adjusted international prognostic index. The working formulation and Kiel classification were used to classify lymphoma at the time of enrollment and the tumours were reclassified according to the WHO classification. Patients were staged according to Ann Arbor classification. Performance status was assessed according to the Eastern Cooperative Oncology Group Scale.

In the Chemotherapy alone arm, patients received - three cycles of ACVBP (doxorubicin 75mg/m^2, cyclophsphamide 1200mg/m^2 on day 1, vindesine 2mg/m^2 and 10mg of bleomycin on day 1 and 5, and prednisone 60mg/m^2 on day 1 through 5) given at 2 weeks intervals and followed by sequential consolidation consisting of two cycles of methotrexate (3gm/m^2) + leucovorin rescue, four cycles of etoposide (300mg/m^2) and ifosfamide (1500mg/m^2) and two cycles of cytaraibine (100mg/m^2) subcutaneously for four days given at two-week intervals. In the Chemoradiotherapy arm, patients received three cycles of CHOP (doxorubicin 50 mg/m^2), Cyclophosphamide 750 mg/m^2, vincristine 1.4 mg/m^2 (up to a maximum dose of 2mg) on day 1 and prednisolone 60 mg/m^2 from day 1 to 5) repeated at 21 day intervals. Involved field

radiotherapy began one month after the last cycle of CHOP. The prescribed dose of radiation was 40 Gy in 22 fraction of 1.8 Gy, five days/ week. In neither group, adjustment of the chemotherapy dose planned but courses were postponed until leucocyte and platelets counts increased to greater than 2000 and 100,000/mm^3, respectively. Patient could receive G-CSF at the investigators discrimination.

Response was evaluated one month after the completion of treatment, according to International Workshop criteria.[8] The main characteristics of the patients were similar in the two groups. DLBCL was the most common subtype and extranodal involvement was found in 49% of patients.

At a median follow up of 7.7 years, event-free and overall survival rates were significantly higher in the group given chemotherapy alone than in the group given CHOP plus radiotherapy ($p<0.001$ and $p<0.001$, respectively). The five year estimated event free survival was 82 percent (95% CI: 78 to 87% for patients receiving chemotherapy alone versus 74% (95 % CI: 69 to 78%) for those receiving chemotherapy. The respective five year estimates of overall survival were 90 percent (95% CI, 87 to 93%) and 81% (95% CI, 77 to 86%. In a multivariate analysis event-free and overall survival rates were affected by treatment group, independently of tumour stage and the presence or absence of bulky disease.

There was no treatment related deaths. Thirty four episodes of grade 3 infection (11% of patient) and two episodes of grade 4 infection (1%) occurred in the chemotherapy group, as compared with four episodes of grade 3 infection in the chemoradiotherapy group (1%). No life-threatening acute adverse effects of radiotherapy were recorded.

COMMENTS

Present study has confirmed that for patients under 61 years of age with localized low risk, aggressive NHL, chemotherapy with three cycles of ACVBP followed by sequential consolidation is adequate and is superior to three cycles of CHOP plus radiotherapy for the treatment. For prognostication, IPI (international prognostic score) was used. IPI scoring is familiar to most clinicians and uses 5 risk factors to predict outcome including age, stage, LDH, PS and number of extra-nodal sites of disease. However, a minor modification termed as Stage modified IPI have been suggested.[6]

Table–1: Adverse risk factors for the IPI and stage-modified IPI compared for use in limited stage lymphoma (adapted from ref.6)

Adverse risk factors	IPI	Stage modified IPI
Stage	III and IV	Non bulky II
AGE	>60	>60
LDH	>normal	>normal
PS	£2	£2
Extranodal sites	£2	Not applicable

The positive point of this study is that ACVBP protocol is better than CHOP (3) + RT for the treatment of low-risk aggressive localized lymphoma. In this trial the increased doses and reduced intervals between the three courses of ACVBP increased the theoretical dose intensity of doxorubicin and cyclophosphamide as compared with three cycles of CHOP. RT was not used in the ACVBP arm , inherent complications of RT could be avoided like second cancers, which may be increased in long term follow-up. There is increased response rate but without the increased mortality rate.

However, ACVBP combination is a very intensive regimen and there is higher toxicity, like-incidence of grade 3 neutropenia (11% in ACVBP vs 1% in CHOP + RT arm). Although the regimen was used on out patient basis and the hospitalization rate is not mentioned in the study, considering the higher rate of neutropenia, the actual hospitalization rate and cost of therapy will be probably higher. Contrary to this the CHOP + RT regimen is cheaper and simpler.

Although the majority of patients with low risk localized aggressive lymphoma can be cured using a brief course of doxorubicin containing chemotherapy followed by involved-field RT, there is room for improvement. Widely available studies combining targeted drugs with standard treatment offer patients a very real possibility of improved outcome. Given the benefit of the combination of rituximab and chemotherapy,[9] this group has undertaken a trial of rituximab plus the ACVBP regimen in young adults with localized low-risk aggressive lymphoma; results of this study are awaited. Whether patterns of gene and protein expression might allow the identification of subgroups of patients most likely to benefit from a particular intensive regimen, such as ACVBP remain to be explored.

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