Chemotherapy for older patients with newly diagnosed, advanced-stage, aggressive-histology non-Hodgkin lymphoma: a systematic review

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Authors' objectives
To assess chemotherapeutic regimens in patients of at least 60 years of age with previously untreated, advanced-stage, aggressive-histology non-Hodgkin lymphoma.

Searching
The following databases were searched: MEDLINE from 1966 to April 2000; EMBASE from 1980 to March 2000; Cancerlit from 1983 to April 2000; Current Contents from 1993 to April 2000; Best Evidence from 1991 to April 2000; the Cochrane Library (Issue 1, 2000); and UMI ProQuest. Tables of contents of haemato-oncology journals, and the reference lists from retrieved articles and textbooks, were also searched. Studies reported in any language were considered. Abstracts were excluded from the review.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) comparing different chemotherapy regimens were included in the review. Evidence-based practice guidelines were also included. Subset analyses were included if they contained data on the subset of patients aged 60 years or older.

Specific interventions included in the review
Anthracycline-containing regimes, such as CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) and CTVP (cyclophosphamide, pirarubicin, vincristine and prednisone) were compared with the following:

a regimen that omitted the anthracycline, i.e. CVP (cyclophosphamide, vincristine and prednisone);

a regimen that used a substituted anthracycline, e.g. CNOP (cyclophosphamide, mitoxantrone, vincristine and prednisone) (the paper provided more examples);

a different dosage regimen, i.e. one-third dosages administered weekly;

a regimen designed to be less toxic, i.e. VMP (teniposide, mitoxantrone and prednimustine); or

second- and third-generation regimens, e.g. ProMACE-CytaBOM, MACOP-B or m-BACOD (the paper provided further details).

There were also comparisons of other types of regimes, e.g. BEP (bischloroethylnitrosourea, etoposide and procarbazine) versus MEP (mitoxantrone, etoposide and prednisone), and of third-generation regimes, e.g. ProMECE-CytaBOM versus MACOP-B; further details were provided in the paper. The dosages were not stated. Studies that used interferon, maintenance chemotherapy or stem cell transplantation, were excluded.

Participants included in the review
Patients aged at least 60 years. These had to have previously untreated, advanced-stage (any stage with B symptoms, and stages II to IV on the Ann Arbor staging system), aggressive-histology (intermediate or high grade according to the National Cancer Institute's working formulation) non-Hodgkin lymphoma. Participants with human immunodeficiency virus-related lymphoma were excluded from the study.

Outcomes assessed in the review
The outcomes of interest were the response rate (complete response and overall response), survival and toxicity.
How were decisions on the relevance of primary studies made?
Two reviewers, blinded to the authors' names and institutional affiliations, journal name, publication year, and study results, independently reviewed the retrieved citations from MEDLINE, Cancerlit and EMBASE. Any disagreements were resolved by a third reviewer. One reviewer, unblinded, assessed the citations from the other databases.

Assessment of study quality
Validity was assessed using the 3-item, 5-point scale of Jadad et al. (see Other Publications of Related Interest). One author abstracted the study quality score.

Data extraction
One author abstracted data on the characteristics of the patients, the study quality score, survival, disease response and control, toxicity, and quality of life. The data extracted and tabulated included the following: study identification; type of analysis (primary or subgroup); age; sample size; disease stage; pathology; chemotherapy regimen; principle tested; disease response; disease control; and overall survival.

Methods of synthesis
How were the studies combined?
A narrative synthesis was undertaken.

How were differences between studies investigated?
The studies were grouped according to whether the study made comparisons of the following: regimens that differed only in the specific anthracycline agent used; a fractionated chemotherapy schedule with the standard schedule for the same chemotherapy; or regimens that differed by some other criteria. Studies were presented separately, with information presented on the quality score, baseline characteristics, whether the data were analysed on an intention to treat basis, and whether sample size calculations were presented.

Results of the review
Twelve RCTs (1,429 participants) were included in the review.

The inter-observer \( K \) was 0.83. The intra-observer \( K \) values for each of the blinded assessors were 0.60 and 0.80 (based on 20 randomised citations from MEDLINE).

Of the 12 included studies, 3 received a quality score of 3, 8 received a score of 2, and one received a score of 1.

Comparisons testing regimens with anthracycline substitution (4 studies).

One study reported results favouring CHOP over a similar regimen that substituted mitroxantrone for doxorubicin (CNOP). One study suggested that a regimen using epirubicin (CEOP-Bleo; cyclophosphamide, epirubicin, vincristine, prednisone and bleomycin) was beneficial compared with a similar regimen (CIOP-Bleo) that substitute idarubicin for epirubicin. Another study lacked sufficient power to determine whether any differences could be detected, and in a subgroup analysis, the complete response rate did not differ between groups assigned to a regimen that contained epirubicin compared with one that contained doxorubicin.

Comparisons testing regimens with chemotherapy schedule fractionation (1 study).

Only one study examined a conventional CHOP regimen (full doses given every 3 weeks), compared with a dose-modified regimen of one-third doses administered weekly. Although no difference in 2-year progression-free survival was detected, the 2-year overall survival was of borderline significance in favour of CHOP \((P=0.05)\).

Comparisons of regimens differing by other criteria (7 studies).

Four studies compared CHOP with another regimen, whilst the other three studies compared regimens that did not
include CHOP. Of the studies that examined CHOP, one found that patients receiving CHOP had lower rates of progression-free survival, overall survival, progression and relapse of lymphoma, but significantly more toxicity. Three subgroup analyses compared the use of CHOP with the use of second- and third-generation regimens. Differences were not detected in failure-free or overall survival. Patients receiving CTVP had improved outcomes compared with CVP, whilst another study that compared BEP with MEP was underpowered. A subgroup analysis showed no difference in complete response rate in patients assigned to one of two third-generation regimens (i.e. ProMECE-CytaBOM versus MACOP-B).

Authors' conclusions
Compared with other regimens, an anthracycline-containing regimen such as CHOP, given in standard doses and schedule, provides superior outcomes for the treatment of older patients with advanced-stage, aggressive-histology lymphoma who do not have significant co-morbid illnesses. Treatment with CHOP was associated with improvements in disease control and survival, but also with greater toxicity.

CRD commentary
The review question and the inclusion and exclusion criteria were clearly stated. Several databases were searched, some unpublished literature was sought, and there were no language restrictions, thus minimising publication bias. The search terms were not provided in the paper, although it was stated that the details are available from the authors on request. Details of the individual studies were presented, although some were lacking in information such as the mean age and the sample size by treatment group.

The validity of the included studies was assessed and reported. However, the authors explicitly state that the score was not used to determine study inclusion or the quantitative weighting of the results. In addition, five of the twelve studies were subgroup analyses. Without an additional assessment of these subgroup analyses, it is difficult to know whether their results are valid. While the studies were summarised appropriately using a narrative synthesis, and the conclusions appear to follow from the results, the conclusions should be interpreted with caution given the lack of high-quality studies.

Implications of the review for practice and research
Practice: The authors state that, in the absence of significant co-morbid illness or strong patient preferences, age should not be used as a variable to modify therapy. In addition, older patients with newly diagnosed, advanced-stage, aggressive-histology non-Hodgkin lymphoma should be offered the same standard therapy as younger patients, namely CHOP.

Research: The authors state that the role of pirarubicin or epirubicin in a CHOP regimen, compared with that of doxorubicin, is unknown; well-designed studies comparing standard doses of the different anthracyclines are needed. The evidence indicated that CHOP (or CTVP) should be the standard against which new treatments are compared in older patients. In addition, further research is needed to explore treatment strategies in older patients with co-morbid illnesses.

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