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CRD summary
This review found benefits in overall survival with use of dose-dense treatment schedules compared to standard treatment schedules in early stage breast cancer and non-Hodgkin's lymphoma in some trials. A lack of information regarding study quality means the reliability of the authors’ conclusions is unclear.

Authors' objectives
To evaluate the impact of dose-dense regimens on clinical outcomes in breast cancer, non-Hodgkin lymphoma and non-small cell lung cancer.

Searching
MEDLINE, EMBASE, CancerLit and The Cochrane Library were searched for relevant studies published in English between January 1995 and October 2010; search terms were reported. Reference lists from clinical trials and review articles were checked to identify additional references.

Study selection
Clinical trials that evaluated dose-dense chemotherapeutic regimens to standard chemotherapeutic regimens in patients with breast cancer, non-Hodgkin lymphoma or non-small cell lung cancer were eligible for inclusion. Dose-dense regimens were defined as regimens where the interval between treatment cycles were decreased while drugs and total doses of the drugs per treatment were the same as the other regimens in the trial. Eligible trials were required to report any of overall survival, progression-free survival and time to disease progression or complete, total or partial response. Studies of exclusively paediatric populations and studies that involved peripheral blood stem cell transplantation and studies that reduced or increased drug doses per treatment were excluded from the review.

The trials were conducted in Europe, the United States, Japan and China. Most trials compared every three week schedules to every two week treatment regimens. Trials in non-small cell lung cancer compared every three week schedules to every four week schedules. A wide range of chemotherapeutic drugs were used including doxorubicin, cyclophosphamide, paclitaxel, methotrexate, fluorouracil, epirubicin and mitoxantrone. Cisplatin-based therapy was used in the trials in non-small cell lung cancer. The use of growth factor support and interval modifications varied across the trials.

Two reviewers performed the study selection; any disagreements were resolved by consensus with four reviewers.

Assessment of study quality
The authors did not state they assessed methodological quality.

Data extraction
One reviewer extracted data on overall survival, progression-free survival and time to disease progression or complete, total or partial response. Data were checked for completeness and accuracy by two additional independent reviewers. The extracted results were stratified by disease type.

Methods of synthesis
The results were summarised in a narrative synthesis by cancer type, outcome and time point.

Results of the review
Fifteen randomised controlled trials were included in the review: eight studies of breast cancer (early-stage breast cancer 3,453 participants and advanced breast cancer 377 participants), four studies of non-Hodgkin lymphoma (2,001 participants) and three studies of patients with non-small cell lung cancer (333 participants).
Early or node-positive breast cancer: One of four trials that evaluated overall survival reported statistically significant benefits at four years with dose-dense treatment (RR 0.69, 95% CI 0.50 to 0.93; 2,005 participants). One trial (150 participants) assessed progression-free survival but no differences between standard and dose-dense regimens were found. There were no differences in response rates between regimens in two trials.

Advanced or metastatic cancer: No differences were observed in overall survival (three trials) or progression-free survival (three trials) between dose-dense treatment groups and standard treatment groups. Two of four trials (256 participants) that reported response rates found significantly higher complete response rates with dose-dense treatment schedules.

Non-Hodgkin lymphoma: Two of four trials that evaluated overall survival found significant benefits with dose-dense schedules compared to standard treatment schedules (1,697 participants). All four trials provided data on response rates that generally favoured dose-dense schedules, although significant benefits in complete response were found in one trial (831 participants).

Non-small cell lung cancer: One trial (100 participants) showed improved median survival (57 weeks compared to 37.7 weeks, p=0.036) and improved median progression-free survival (23.7 compared to 13.9 weeks) with dose-dense treatment. Rates of complete responses were low in all the trials and no differences in complete or partial response were observed.

Authors’ conclusions
Benefits in overall survival were observed in some trials in potentially curative settings in early-stage breast cancer and non-Hodgkin’s lymphoma with dose-dense treatment schedules compared to treatment using standard schedules. Most of the trials were small with insufficient statistical power and significant differences between groups were reported in only a few trials.

CRD commentary
The review addressed a clear question. Criteria for inclusion of studies were defined and reproducible. Appropriate databases were searched for relevant studies. The restriction to studies published in English and the lack of a search for unpublished studies risked language and publication biases. The reviewers took steps to minimise errors and biases for study selection and data extraction. The methodological quality of the included studies was not assessed and this made it difficult to make a judgement regarding the reliability of the results. It was not clear how many patients were lost to follow-up so the reliability of the survival data was unclear. The authors’ decision to summarise the results in a narrative synthesis appeared to be justified because of the clinical heterogeneity present across the included studies.

In general, the reliability of the authors’ conclusions is not clear and the conclusions should be interpreted with some caution because of the lack of information on study quality in the included studies.

Implications of the review for practice and research
Practice: The authors stated that patients and clinicians needed to consider the benefits, harms and costs of dose-dense chemotherapy regimens.

Research: The authors stated that further research in large randomised controlled trials of dose-dense schedules was required to determine consistency and of the findings from the review, particularly across other types of cancer.

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