Timing of first-line cancer treatments - early versus late: a systematic review of phase III randomized trials

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CRD summary
This review compared the efficacy of early versus late first-line treatments for cancer and concluded that delaying treatments did not have an adverse effect on survival in the cancer types studied except in prostate cancer. These conclusions should be interpreted with caution, given the possibility of missing potentially relevant studies, risk of language bias and limited quality of included trials.

Authors' objectives
To compare the efficacy of early versus late first-line treatment for cancer.

Searching
MEDLINE and the Cochrane Library were searched from 1966 to 2008. Search terms were reported. Reference lists from relevant publications were screened. Experts in the field were contacted to identify additional relevant studies. Studies not in English were excluded.

Study selection
Phase III randomised controlled trials (RCTs) that compared early versus late first-line treatment of cancer were eligible for inclusion. The review outcomes were overall survival, progression-free-survival and response rate.

Most included trials were of patients with prostate cancer and multiple myeloma; the remaining trials were of patients with lung cancer, follicular (non-Hodgkin’s) lymphoma and chronic lymphocytic leukaemia. The included patients received various types of treatments, including chemotherapy, endocrine and radiation. The disease stage of included patients varied between trials. Where reported, the median age of patients ranged from 52 to 73 years. Most trials defined ‘early’ treatment as immediate treatment on diagnosis/randomisation and ‘late’ treatment as that given on symptomatic disease progression. The included trials were published between 1990 and 2006.

Two reviewers independently assessed studies for inclusion, with any disagreement resolved by consensus.

Assessment of study quality
The quality of included trials was assessed using criteria for randomisation, allocation concealment, blinding of outcome assessors, intention-to-treat analysis, sample size calculation, and withdrawals.

It appeared that two reviewers performed quality assessment.

Data extraction
Data were extracted on event rate, to calculate hazard ratios (HRs) or risk ratios (RRs) with 95% confidence intervals (CIs). Where time-to-event data were not available, the method by Parmar et al. was used to calculate hazard ratios using indirect calculation of the variance and the number of observed minus expected events.

It appeared that two reviewers performed data extraction.

Methods of synthesis
The trials were combined in meta-analyses. Pooled hazard ratios or risk ratios, with 95% confidence intervals, were calculated using a random-effects model. Separate analyses were performed for different types of cancer. Statistical heterogeneity was assessed using $X^2$ and $I^2$. Sensitivity analyses were conducted on the basis of trial quality. Publication bias was assessed using a funnel plot.
Results of the review
Ten phase III RCTs were included in the review (n=3,811 patients): three RCTs of prostate cancer, three RCTs of multiple myeloma, two RCTs of chronic lymphocytic leukaemia, one RCT of lung cancer, and one RCT of follicular lymphoma. Four trials reported the method of randomisation. Allocation concealment was adequate in five trials. None of the trials reported blinding of outcome assessors. Eight trials used intention-to-treat analyses. Six trials provided the description of withdrawals. Three trials reported the sample size calculation.

Overall survival: Early first-line treatment was associated with a significant benefit in overall survival in patients with prostate cancer compared with late first line treatment (HR 1.23, 95% CI 1.11 to 1.37; three RCTs). There was no significant difference in overall survival between the two early and late treatment in multiple myeloma, chronic lymphocytic leukaemia, follicular lymphoma or lung cancer.

Progression-free survival: Compared with late first-line treatment, early first-line treatment was associated with a significant benefit in progression-free survival in patients with prostate cancer (HR 1.67, 95% CI 1.37 to 2.05; two RCTs, three comparisons), chronic lymphocytic leukaemia (HR 1.95, 95% CI 1.19 to 3.21; two RCTs) and multiple myeloma (HR 4.39, 95% CI 1.82 to 10.56; two RCTs). There was no significant benefit in progression-free survival with early first-line treatment in follicular lymphoma.

Response rate: There was no significant difference in response rate between early and late treatment for patients with multiple myeloma, chronic lymphocytic leukaemia or lung cancer.

No significant heterogeneity was observed in any of these outcomes. Sensitivity analyses did not materially alter the results.

There was no evidence of publication bias.

Authors' conclusions
Delaying cancer treatment did not necessarily compromise therapeutic outcomes except possibly in patients with prostate cancer.

CRD commentary
The inclusion criteria of the review were clear. Only two databases were searched, so potentially relevant studies may have been missed. Efforts were made to find published studies, but no attempts were made to locate unpublished studies, which increased the potential for publication bias. The possibility of publication bias was assessed and little evidence was found. The decision to restrict the review in English studies may have increased the risk of language bias. It appeared that steps were made to minimise reviewer biases and errors in the review process.

Appropriate criteria were used to assess trial quality. Statistical heterogeneity was assessed and appropriate methods were used to pool the results. The authors acknowledged that the review included patients with three types of cancers which were not the most common, so the findings may be not generalisable to patients with other types of cancers.

The authors' conclusions were supported by the data identified. However, these conclusions should be interpreted with caution, given the possibility of missing potentially relevant studies, the risk of language bias and the limited quality of included trials.

Implications of the review for practice and research
Practice: The authors stated that the findings from this review provided a unique window to oncologists and patients to address time-sensitive issues.

Research: The authors stated that further clinical trials with a large sample size for specific cancer types (e.g. breast and colon cancer) were required to provide a definitive answer on whether delaying treatment had an adverse effect on survival for cancer patients.
Funding
None.

Bibliographic details

PubMedID
20444550

DOI
10.1016/j.ctrv.2010.04.001

Original Paper URL
http://www.cancertreatmentreviews.com/article/S0305-7372(10)00078-2/abstract

Indexing Status
Subject indexing assigned by NLM

MeSH
Antineoplastic Combined Chemotherapy Protocols /therapeutic use; Clinical Trials, Phase III as Topic; Disease-Free Survival; Female; Humans; Leukemia, Lymphocytic, Chronic, B-Cell /mortality /pathology /therapy; Lung Neoplasms /mortality /pathology /therapy; Male; Multiple Myeloma /mortality /pathology /therapy; Neoplasms /mortality /pathology /therapy: Prognosis; Prostatic Neoplasms /mortality /pathology /therapy; Radiotherapy, Adjuvant; Risk Assessment; Survival Analysis; Time Factors; United States

AccessionNumber
12010008072

Date bibliographic record published
15/06/2011

Date abstract record published
07/12/2011

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.