Interferon alfa versus chemotherapy for chronic myeloid leukemia: a meta-analysis of seven randomized trials

Chronic Myeloid Leukemia Trialists' Collaborative Group

Authors' objectives
To assess the difference in survival of patients treated with interferon (IFN)-alpha or standard chemotherapy, and to establish whether any such difference is greater in a particular patient group.

Searching
MEDLINE and other sources (unspecified clinical trial databases) were searched. Meeting abstracts, reference lists and review articles were checked, and experts and pharmaceutical companies were contacted.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) that began before 1990 were eligible for inclusion in the review.

Specific interventions included in the review
Trials comparing IFN-alpha with standard chemotherapy (busulfan or hydroxyurea) were to be reviewed. The included studies utilised doses of 2 to 9 MU/day IFN-alpha.

Participants included in the review
Studies of patients with chronic myeloid leukaemia were to be reviewed. Studies that included both Philadelphia (Ph) chromosome-positive and -negative patients were eligible for inclusion. No demographic details of the patients in the included studies were given in the review.

Outcomes assessed in the review
The primary outcome measure of interest in the review was annual mortality rate.

How were decisions on the relevance of primary studies made?
Contact with the individual trialists was made to ensure the data were being interpreted correctly.

Assessment of study quality
This review was conducted on individual patient data (IPD). The data were checked for obvious inconsistencies, for balance between treatments within different subgroups and over time, and for apparent discrepancies with any publications. As far as possible, data were to be obtained for all of the patients randomised. Individual trialists were sent tabulations of their own data for checking. The authors do not mention any trials excluded from the review on the grounds of validity.

Data extraction
Once a relevant trial was identified, data on each individual patient were sought. The authors do not state how they obtained the IPD. The IPD included gender, Ph chromosome positivity, platelet and white blood cell counts, Sokal score at diagnosis, dates of birth, diagnosis, and randomisation. The follow-up variables included date last seen alive, date and type of response, date and type of any bone marrow transplant, and date and cause of death.

Methods of synthesis
How were the studies combined?
An intention-to-treat analysis was performed with patients compared on the basis of their randomly allocated treatment.
Log rank survival analyses for each trial yielded, for the IFN alpha-allocated group, the observed and the expected numbers of deaths, and the variance of the difference between these for each trial. These were then summed, one per trial, and used to calculate the death rate ratio to the hazard function ratio. The death rate ratios were described in terms of the percentage odds reductions, and all p-values were two-sided.

How were differences between studies investigated?
A chi-squared analysis was used to formally test for heterogeneity in the meta-analyses.

Results of the review
Eleven eligible trials (2,189 patients) were identified, but data were available for only seven of them (1,982 patients). Thus, about 90% of the total number of patients studied were actually included in this IPD analysis.

In most trials, the main analysis included only Ph chromosome-positive patients. However, since the number of patients not known to be Ph-positive was small, their inclusion or exclusion had no material effect on the overall result.

The overall reductions in the annual death rate were 36% (standard deviation, SD=9; p=0.00007) for IFN versus busulfan, 26% (SD=8; p=0.001) for IFN versus hydroxyurea, and 30% (SD=6; p<0.00001) for IFN versus hydroxyurea or busulfan.

The cumulative effect on survival was to prolong survival by one or two years. In addition, there was an improvement in the 5-year survival rates from 42% with chemotherapy to 57% with IFN-alpha, an absolute difference of 15% (SD=3; p<0.00001). The absolute improvement in the 5-year survival rate was 20% (SD=5) in the trials of IFN-alpha versus busulfan, and 12% (SD=4) in the trials of IFN-alpha versus hydroxyurea.

There were no trials or subgroups of patients in which the treatment difference was statistically significantly different from the average.

Authors’ conclusions
The authors concluded that 'For patients with Ph chromosome-positive chronic myeloid leukaemia, the inclusion of IFN-alpha in the therapeutic regimen produced a substantially better five-year survival than standard chemotherapy alone'.

CRD commentary
The review addressed a relevant clinical question using clear inclusion and exclusion criteria. The search for relevant studies was not described in detail in the review, making it difficult to be completely confident that important studies were not missed. Collecting IPD for meta-analysis has several advantages over the usual method of simply combining the overall study results. However, studies can be excluded if additional patient data are not forthcoming. In the present study four trials were excluded from the analyses on such grounds, but since the patient numbers were relatively small in these trials, their exclusion was unlikely to have had a pronounced effect on the overall estimates. It would have been useful to have known the overall results of each of the studies for which IPD were not obtained. The conduct of this IPD review appears to have been good with the data checked. However, further information on how the data were obtained should have been reported. The analysis of the data was performed appropriately and, overall, this was a good review and the authors’ conclusions appear valid from the data presented.

Implications of the review for practice and research
Practice: The authors state that it is not yet clear what the dosage or duration of IFN-alpha should be, or how best to combine IFN-alpha with chemotherapy.

Research: The authors did not state any implications for further research.

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