Interferon alfa versus interferon alfa plus cytarabine combination therapy for chronic myeloid leukemia: a meta-analysis of randomized controlled trials

Chen R, Ma B, Yang K, Tian J, Liu Y, Zhao L

CRD summary
The review concluded that compared with interferon alpha alone, combined interferon alpha plus cytarabine significantly improved complete haematologic response and cytogenic response rates and improved three-year and five-year survival, but was more likely to cause serious adverse events. The reviewers’ conclusions should be considered tentative due to potential for bias and the poor quality evidence base.

Authors' objectives
To compare the effects of interferon-alpha (IFN-alpha) plus cytarabine versus IFN-alpha alone in chronic myelogenous leukaemia.

Searching
PubMed, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), Chinese Biomedical Database, China National Knowledge Infrastructure and Chinese Scientific Journals Database were searched for relevant studies published in English or Chinese; search terms were reported. Reference lists of retrieved studies were searched.

Study selection
Randomised controlled trials (RCTs) of patients diagnosed with chronic myelogenous leukaemia who were positive for the Philadelphia chromosome and had not previously been treated with chemotherapy (including hydroxyurea, busulfan and IFN-alpha) were eligible for the review. Studies were excluded if they contained participants with features of accelerated or blast phases of chronic myelogenous leukaemia. Also excluded were studies with participants who had a history of depressive illness or another psychiatric disorder or severe hepatic, renal or cardiovascular disorders, were aged more than 70 years or had initially failed to respond to tyrosine kinase inhibitor treatments. Studies were required to compare IFN-alpha plus cytarabine with IFN-alpha alone. Eligible outcomes included complete haematologic response, cytogenic response, major cytogenic response, complete cytogenic response, partial cytogenic response, three-year and five-year survival rates and toxicities and adverse effects.

Participants in the included studies were 18 years or older. Intervention medication regimens varied: IFN-alpha dosage ranged from 5MU/m² to 56IU/m² and cytarabine absolute dose varied from 20mg/m² to 40mg/m².

Two reviewers selected studies for the review.

Assessment of study quality
Studies were assessed for quality according to Cochrane criteria of randomisation, double blinding, allocation concealment and withdrawal/follow-up.

Two reviewers independently assessed studies for quality. Disagreements were resolved by consensus.

Data extraction
Data were extracted on the outcomes. Relative risks (RRs) were calculated for dichotomous outcomes and mean differences were calculated for continuous outcomes, each with 95% confidence intervals (CIs). Where necessary, authors were contacted for clarification of data.

Data were extracted by one reviewer and checked independently by a second reviewer.

Methods of synthesis
Studies were pooled in meta-analyses, where possible. A random-effects model was used where there was evidence of heterogeneity (I² > 50%) and a fixed-effect model was used (no evidence of heterogeneity). Summary effect risk ratios, weighted mean differences (WMDs) and standardised mean differences (SMDs), with 95% CIs, were calculated.
Heterogeneity was assessed with $\chi^2$ and $I^2$. Publication bias was assessed using the funnel plot method for the primary endpoints.

**Results of the review**

Four RCTs (3,139 participants, range 538 to 1,340) were included in the review. Only one of the studies described the randomisation process, had adequate allocation concealment and used intention-to-treat analysis. One other study reported blinding. Follow-up ranged from six months to years.

**Primary outcomes:** Compared to IFN-alpha alone, combined treatment with IFN-alpha plus cytarabine was associated with a significantly better complete haematologic response (RR 1.15, 95% CI 1.09 to 1.21; four studies), significantly better complete cytogenetic response (RR 1.87, 95% CI 1.47 to 2.38; four studies), significantly better partial cytogenetic response (RR 1.48, 95% CI 1.25 to 1.75; four studies) and major cytogenetic response (RR 1.61, 95% CI 1.42 to 1.83; four studies). Compared to IFN-alpha alone, combined IFN-alpha plus cytarabine was associated with significantly increased three-year survival (RR 1.09, 95% CI 1.03 to 1.14; two studies) and five-year survival (RR 1.08, 95% CI 1.01 to 1.15; two studies). No heterogeneity was identified.

**Secondary outcomes:** Compared to IFN-alpha alone, combined IFN-alpha plus cytarabine was associated with a higher risk of haematologic toxicity (RR 2.63, 95% CI 1.94 to 3.56), gastrointestinal events (RR 3.38, 95% CI 2.28 to 5.00), severe mucositis (RR 8.84, 95% CI 3.82 to 20.46), weight loss (RR 2.0, 95% CI 1.47 to 2.73) and skin rash (RR 3.75, 95% CI 2.13 to 6.59) in three studies. There were no significant differences between groups in rates of other adverse events, such as fever, flu-like syndrome, neurologic symptoms, psychiatric disorder and hepatic events. No heterogeneity was identified, except in the analysis of weight loss ($I^2=55\%$).

There was no evidence of publication bias.

**Authors’ conclusions**

Compared with IFN-alpha alone, combined IFN-alpha plus cytarabine significantly improved complete haematologic response and cytogenetic response rates and improved three- and five-year survival, but was more likely to cause serious adverse events.

**CRD commentary**

The review addressed a clear research question supported by appropriate inclusion criteria. A wide range of sources was used to search for relevant studies. The restriction to publications in English and Chinese meant that language and publication biases could not be ruled out. Formal assessment of publication bias by inspection of funnel plots revealed no evidence, but this result may not be reliable due to the small number of studies. Appropriate methods were used to select studies, make quality assessments and extract data, which minimised the chance of reviewer error and bias. The evidence base was limited to four studies that were generally of poor to intermediate quality. Few details were provided on the types of participants in the included studies and interventions used different doses and varying medication regimens.

The reviewers’ conclusions should be considered tentative due to potential for bias and the poor quality evidence base.

**Implications of the review for practice and research**

**Practice:** The authors stated that combined IFN-alpha plus cytarabine may be the first choice for chronic myelogenous leukaemia patients in developing countries.

**Research:** The authors stated a need for large well-designed studies with long-term follow-up to determine effects on survival, duration of response, development of resistance and safety. Research should focus on specific subgroups, such as accelerated or blast phase of chronic myelogenous leukaemia patients, the elderly, children And those eligible for bone marrow transplantation and should measure quality of life and cost effectiveness.

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