A systematic collaborative overview of randomized trials comparing idarubicin with daunorubicin (or other anthracyclines) as induction therapy for acute myeloid leukaemia

AML Collaborative Group

Authors' objectives
To compare idarubicin versus daunorubicin, or other anthracyclines, when used with cytosine arabinoside as induction chemotherapy for newly diagnosed acute myeloid leukaemia (AML).

Searching
The authors searched MEDLINE and PDQ; no search dates or search terms were provided. It was implied that more databases were searched, but no details were provided. The authors searched publications, meeting abstracts and lists of protocols through computer-assisted searching or handsearches. They also contacted trialists and pharmaceutical companies. A collaborative group (the AML Collaborative Group) was established to undertake the meta-analysis.

Study selection
Study designs of evaluations included in the review
The review included individual patient data (IPD) from randomised controlled trials (RCTs).

Specific interventions included in the review
Specific inclusion criteria for the interventions were not stated. The interventions included in the review were idarubicin (8 to 20 mg/m2 per day) compared with daunorubicin (45 to 50 mg/m2 per day), doxorubicin (30 mg/m2 per day), or zorubicin (200 mg/m2 per day). The participants also received cytosine arabinoside (Ara-C)(100 to 200 mg/m2 per day).

Participants included in the review
Specific inclusion criteria for the participants were not stated. The participants had newly diagnosed AML. In the idarubicin versus daunorubicin trials, 53% of the participants were males and 54% were older than 60 years of age.

Outcomes assessed in the review
Specific inclusion criteria for the outcomes were not stated. The outcomes reported in the review were complete remission, relapse, death and overall disease-free survival.

How were decisions on the relevance of primary studies made?
The authors invited trial coordinators of studies that began before 1993 to participate.

Assessment of study quality
The data sets were checked centrally for internal consistency, for consistency with any previous publications, for balance between treatment groups, and for the exclusion of any randomised participants, or the inclusion of any non-randomised participants. If there were any problems, the trialists were contacted so that errors or omissions were rectified where possible. Summary tables of information for each trial were also sent to the trialists for checking. In addition, the review was given to each trial group to ensure the results presented for their trial were correct. The authors excluded studies that began after 1 January 1993. The authors did not state how judgements of validity were made.

Data extraction
The data to be collected for each participant were agreed in consultation with the trialists. Such data included age, gender, nationality, white blood count, performance status, allocated treatment, dates of diagnosis, randomisation, complete remission, first relapse and death. The observed minus the expected number of events, and variance, were calculated for the idarubicin-allocated group within each trial either using simple contingency tables, or by the log rank
test (using the exact dates of relevant events) for analysis of time to failure.

Methods of synthesis
How were the studies combined?
The trials were analysed using intention-to-treat. Mean complete remission and death rates were calculated for the five idarubicin versus daunorubicin trials. The odds ratios (ORs) and odds reduction were calculated for disease-free survival and overall survival for each trial, then a combined OR was calculated with 95% confidence intervals using a meta-analysis. Complete remission rates were examined by age group (younger than 40, 40 to 59, and 60 years and older), gender, white blood count, FAB (French-American-British cytology) type, and performance status.

How were differences between studies investigated?
Three subgroups were examined: idarubicin versus daunorubicin, idarubicin versus doxorubicin, and idarubicin versus zorubicin. The authors investigated statistical heterogeneity using a chi-squared test.

Results of the review
Seven trials that compared idarubicin with daunorubicin were identified; however, IPD were retrieved from only five of these trials (n=1,053). In addition, two trials compared idarubicin with either doxorubicin (n=100) or zorubicin (n=745). The unavailable patient data represented 4% (86 patients) of the total. Another three trials were identified that began after the cut-off date of 1 January 1993; their results were not available at the time the review was conducted. An additional trial was identified that compared idarubicin with daunorubicin, but it was abandoned early because of gastrointestinal toxicity, and the results were not available.

Complete remission: overall, there was a better rate of complete remission with idarubicin than with daunorubicin (62% versus 53%, P=0.002). No significant difference was found in the two trials comparing idarubicin with doxorubicin or zorubicin.

Death or relapse: overall, the proportion of remitters who died in their first remission or relapsed was 84.3% with idarubicin and 87.3% with daunorubicin (log rank P=0.07).

Disease-free survival: in the five idarubicin versus daunorubicin trials, there was no significant difference in disease-free survival (P=0.07). The individual trials of idarubicin versus doxorubicin and zorubicin showed odds reductions of 26% (P=0.3) and 9% (P=0.4), respectively.

Overall survival: in the five idarubicin versus daunorubicin trials, overall survival was significantly better with idarubicin than with daunorubicin (13% versus 9% alive at 5 years, OR 0.86, P=0.03). There was no significant difference in overall survival in the other two trials.

Authors’ conclusions
From the trials reviewed, the authors concluded that induction regimens based on idarubicin achieved better remission rates and better overall survival than those based on daunorubicin.

CRD commentary
The research question was clearly stated but the inclusion criteria were not explicitly reported. Although details of the search strategy were lacking in the report, the collaborative group approach would have helped ensure that all the relevant trials were identified. The IPD data were appropriately checked and analysed. Sufficient data for each of the included studies were tabulated. This appears to be a thorough review and the authors’ conclusions are likely to be reliable.

Implications of the review for practice and research
Practice: The authors stated that, from the trials reviewed, it was not possible to determine reliably whether idarubicin
is better or worse than doxorubicin or zorubicin.

Research: The authors mentioned that ongoing trials of intensive induction therapy will be included in future updates of this review.

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