A network meta-analysis of randomized controlled trials of induction treatments in acute myeloid leukemia in the elderly

Ziogas DC, Voulgarelis M, Zintzaras E

CRD summary
This review concluded that all-trans retinoic acid or lomustine might be an effective addition but most induction regimens for acute myeloid leukaemia treatment had similar efficacy in elderly patients. The authors cautioned about the extent of the reliance on indirect comparisons. Potential selection biases and uncertain quality of the included trials may reduce the reliability of the conclusions.

Authors' objectives
To estimate the effectiveness of induction treatments in acute myeloid leukaemia in elderly patients.

Searching
PubMed, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched up to September 2010. References of identified studies and relevant reviews were checked for further studies. Search terms were reported. Only published studies reported in full in English were eligible for inclusion.

Study selection
Randomised controlled trials (RCTs) that compared two or more different induction treatments in elderly patients aged at least 60 years with acute myeloid leukaemia were eligible for inclusion in the review. Trials of consolidation and maintenance therapies were excluded. Also excluded were studies that included patients with acute promyelocytic leukaemia or patients with refractory or relapsed acute myeloid leukaemia. Trials with age-stratified populations that included younger age groups were included where separate data were available for those aged over 60. The primary outcome was complete remission; secondary outcomes were median disease-free and overall survival and induction deaths per treatment. Induction myelotoxicity was reported. Definitions of outcomes were reported in the paper.

Included trials assessed a substantial number of different induction regimes. Most comparisons were assessed by only one study. Daunorubicin and cytarabine were the most commonly used components of treatment regimens. The median age of patients was 68 years. Eighteen per cent of patients had secondary acute myeloid leukaemia, 21.1% of patients had poor performance status (range 4% to 37%) and 26.7% had unfavourable cytogenetics (range 15.5% to 46%).

The authors did not state how many reviewers selected the papers for the review.

Assessment of study quality
The authors did not state that they assessed the studies for validity.

Data extraction
Data were extracted on patient characteristics including those with prognostic significance (including median age and proportion with unfavourable cytogenetics or poor performance status). Outcome data were extracted to enable calculation of odds ratios (OR) with 95% confidence intervals (CI).

Two reviewers independently extracted the data; discrepancies were resolved by a third reviewer.

Methods of synthesis
Pooled odds ratios with 95% CI were calculated for the outcome of complete remission using a DerSimonian and Laird random-effects meta-analysis. Statistical heterogeneity was assessed using the Q and I² statistics. Statistical significance of each pairwise comparison in multiple arm trials was assessed separately. Indirect comparisons using results from inverse variance meta-analysis were used to compare treatments in the network.

Results of the review
Sixty-five RCTs (15,110 elderly patients) were included in the review. The median number of patients was 123. Only
six RCTs included more than 500 patients. The included studies assessed 64 direct comparisons between 42 different induction regimens. Overall 7,447 (49.3%) of patients achieved complete remission.

Meta-analysis of 14 direct comparisons was possible; all other direct comparisons were represented by a single trial. Eleven of these meta-analyses showed statistically significant heterogeneity between trial effects. Fourteen of the 64 direct comparisons showed a statistically significant benefit in complete remission (full details given in the paper).

Network meta-analysis indicated a benefit in complete remission for the addition of all trans-retinoic acids (OR 1.93, 95% CI 1.06 to 3.49) or lomustine (OR 1.76, 95% CI 1.08 to 2.88) to idarubicin plus cytarabine. Statistically significantly fewer patients achieved complete remission with no treatment, clofarabine, daunorubicin plus topotecan and two different schedules of gemtuzumab compared with daunorubicin plus cytarabine at standard doses (OR ranged from 0.01 to 0.15; none of the confidence intervals approached 1.00).

There were no statistically significant differences between treatment regimens in induction deaths; incidence of these ranged from 0% to 40%. There were no statistically significant differences between treatments in median disease-free survival (range zero to 23 months) or median overall survival (range 1.1 to 17 months). There was an increase in overall survival with date of trial publications (from 1.8 months in 1976 to 17 months in 2010). There were no statistically significant differences in myelotoxicity or time to hospital discharge.

Authors' conclusions
Compared with the reference induction standard, all-trans retinoic acid or lomustine might be an effective addition to certain regimes although most compared regimens had similar efficacy profiles. The results should be interpreted with caution due to the dominance of indirect comparisons in the network meta-analysis.

CRD commentary
The review question and inclusion criteria were clear. Three relevant databases were searched. The restriction of the review to studies published in English may have led to publication and language biases; a substantial number of potentially relevant studies were excluded because they were not published in English. The authors reported using methods to reduce reviewer bias and error during data extraction but not in study selection. The authors did not report that they assessed the quality of the included trials. The network meta-analysis for the primary outcome appeared appropriate; methods for analysis of secondary outcomes were unclear.

The authors' conclusion reflected the results of the network meta-analysis but their caution about the dominance of indirect comparisons within the network should be noted. The reliability of the conclusions may be impacted by potential selection biases and the uncertain quality of the included trials.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that further in vitro data and larger RCTs in elderly patients with acute myeloid leukaemia were required to establish whether one induction treatment was superior to the alternatives.

Funding
None.

Bibliographic details

PubMedID
21600383

DOI
10.1016/j.clinthera.2011.04.004
Original Paper URL
http://www.clinicaltherapeutics.com/article/S0149-2918(11)00186-X/abstract

Indexing Status
Subject indexing assigned by NLM

MeSH
Aged; Antineoplastic Combined Chemotherapy Protocols /administration & dosage /adverse effects /therapeutic use; Disease-Free Survival; Dose-Response Relationship, Drug; Drug Administration Schedule; Humans; Leukemia, Myeloid, Acute /drug therapy; Randomized Controlled Trials as Topic; Remission Induction; Treatment Outcome

AccessionNumber
12011003663

Date bibliographic record published
12/10/2011

Date abstract record published
05/10/2012

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.