Original Research Article

Conventional and high-dose daunorubicin and idarubicin in acute myeloid leukaemia remission induction treatment: a mixed treatment comparison meta-analysis of 7258 patients†

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Abstract

Previous meta-analyses suggested that acute myeloid leukaemia induction regimens containing idarubicin (IDA) or high-dose daunorubicin (HDD) induce higher rates of complete remission (CR) than conventional-dose daunorubicin (CDD), with a possible benefit in overall survival. However, robust comparisons between these regimens are still lacking. We conducted a mixed treatment comparison meta-analysis regarding these three regimens. Mixed treatment comparison is a statistical method of data summarization that aggregates data from both direct and indirect effect estimates. Literature search strategy included MEDLINE, EMBASE, Cochrane, Scielo and LILACS, from inception until August 2013 and resulted in the inclusion of 17 trials enrolling 7258 adult patients. HDD [relative risk (RR) 1.13; 95% credible interval (CrI) 1.02–1.26] and IDA (RR 1.13; 95% CrI 1.05–1.23) showed higher CR rates than CDD. IDA also led to lower long-term overall mortality rates when compared with CDD (RR 0.93, 95% CrI 0.86–0.99), whereas HDD and CDD were no different (RR 0.94, 95% CrI 0.85–1.02). HDD and IDA comparison did not reach statistically significant differences in CR (RR 1.00; 95% CrI 0.89–1.11) and in long-term mortality (RR 1.01, 95% CrI 0.91–1.11). IDA and HDD are consistently superior to CDD in inducing CR, and IDA was associated with lower long-term mortality. On the basis of these findings, we recommend incorporation of IDA and HDD instead of the traditional CDD as standard treatments for acute myeloid leukaemia induction. The lack of HDD benefit on mortality, when compared with CDD in this study, should be cautiously addressed, because it may have been susceptible to underestimation because of statistical power limitations. Copyright © 2014 John Wiley & Sons, Ltd.

Keywords: acute myeloid leukaemia; anthracyclines; daunorubicin; idarubicin; induction chemotherapy; remission induction

Introduction

Progress in the management of acute myeloid leukaemia (AML) was far from satisfactory throughout the last century. Indeed, a steady yet slow increase in survival was observed over the years, but it was due mainly to the improvement of supportive therapies [1]. Chemotherapy with a combination of an anthracycline and cytarabine remains a thoroughly accepted induction treatment for almost 40 years [2–4]. Daunorubicin (DNR) at a conventional-dose (CDD), that is, in a schedule of up to 180 mg/m² per cycle of chemotherapy, together with cytarabine, in a dosage of 100–200 mg/m² for 5–7 days, is still considered the standard choice, amongst anthracycline derivatives, for de novo adult AML in many hematology–oncology reference centres [5–7].

Several randomized clinical trials (RCTs) compared different anthracycline derivatives and schedules in induction therapy of AML. Previous attempts to compile these studies resulted in few systematic reviews [1,8–10]. In 1998, the AML Collaborative Group observed that idarubicin (IDA), a direct derivative from DNR, could offer a higher rate of complete remission (CR) and overall survival.
(OS) when compared with CDD, although the magnitude of this difference was rather small [10]. In 2011, Ziogas et al. carried out a network meta-analysis on induction treatment of elderly AML patients [1], and concluded that amongst 42 combinations of chemotherapy agents, two regimens showed significant higher rates of CR, both containing IDA (IDA/cytarabine/all-trans retinoic acid and IDA/cytarabine/lomustine). However, no benefit in OS was found. More recently, Teuffel et al. described a meta-analysis on younger patients (including paediatric population) at the same scenario [8]. This study confirmed the superiority of IDA in attaining CR over CDD regimens and found that DNR in higher doses could also lead to higher rates of CR when compared with standard treatment. Moreover, a significant lower rate of overall mortality with high-dose DNR (HDD) could also be ascertained when compared with CDD. Lastly, a meta-analysis by Wang et al. [9] reinforced IDA superiority over DNR, an effect that was due to a benefit found only when compared with the CDD subgroup. Notwithstanding, a consistent meta-analysis performed to compare HDD and IDA regimens is still lacking in a comprehensive adult population.

Therefore, the objective of this study was to conduct a systematic review concerning RCT of induction treatment of adult de novo AML patients evaluating the rate of CR, adverse events and mortality under CDD, IDA and HDD protocols, by means of a mixed treatment comparison (MTC) approach.

Methods

We followed the PRISMA statement for reporting our results [11]. This research has been approved by the ethics committee of our institution and is in accordance with the statements of the Declaration of Helsinki.

Data sources and searches

We performed an electronic literature search on MEDLINE (through PubMed), EMBASE, Cochrane CENTRAL (through Cochrane Wiley), Scielo and LILACS, from inception to August 2013.

In MEDLINE and EMBASE, search strategy included a group of words (both textword and MESH or EMTREE terms) with a high sensitivity for RCT [12–14] and terms related to anthracycline derivative, clinical scenario and patient population. Search strategies in Cochrane CENTRAL, Scielo and LILACS were similar, except for the omission of the strategy for RCT. Detailed information on search strategy for MEDLINE and EMBASE is shown in Table 1.

Study selection

We included all RCTs involving mainly adult patients (age limited to 15 years or older, with no upper limit) with de novo AML undergoing induction treatment that included comparisons of at least two of the following induction regimens: CDD, IDA (any dose) and HDD. We considered CDD as a range from 90 to 180 mg/m² per cycle and HDD as any dose greater than 180 mg/m² per cycle. Selected studies could allow enrollment of patients with acute promyelocytic leukaemia (up to 20%) and secondary leukaemia. Patients could have been exposed to concomitant treatment drugs or therapies but only if it was administered in both treatment arms, allowing a comparison of the isolated effect of the anthracycline schedules studied. Trials should report at least data on the rate of CR attained. We excluded studies that enrolled relapsed AML patients and paediatric population. We have not included, in this study, anthracycline formulations (e.g. liposomal) other than the conventional ones.

Table 1. Search strategy for MEDLINE (August of 2013)

<table>
<thead>
<tr>
<th>Search</th>
<th>Search terms</th>
<th>Number of citations found</th>
</tr>
</thead>
<tbody>
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</tr>
<tr>
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</table>
Title and abstract of each reference identified by the search strategy (after excluding duplicate entries) were evaluated by two investigators in duplicate (including always two reviewers amongst authors L. S., R. A. R. and K. M. L) that applied the predefined eligibility criteria. All abstracts that fulfilled criteria or which exclusion could not be made with the information reported were retrieved for full text evaluation. Full text articles were also reviewed in duplicate. When studies reported on the same cohort of patients (multiple publications), the report with the largest number of patients or longer period of follow up was selected. Definitive inclusion of studies was undertaken only if they effectively complied with inclusion and exclusion criteria and if there was agreement of both reviewers. Disagreements were resolved by consensus or involvement of a third reviewer, if consensus could not be achieved.

Data extraction and quality assessment

Data from all included RCTs were extracted by two investigators in duplicate (including always two reviewers amongst authors L. S., V. D. M. and K. M. L). Data extraction was performed using a standardized electronic data form. When pertinent variables and results were not found in the full text article, further information was pursued on previous systematic reviews that included data from that study. When this approach was unsuccessful, corresponding authors were contacted and asked to provide the aforementioned information.

The primary outcome considered was CR rate (CR defined by each study criteria), by the end of induction (time point defined by each study). Secondary outcomes were CR after the first cycle (FC-CR) of chemotherapy (even if the study allowed additional cycles of induction for initially refractory patients), induction-related mortality, long-term overall mortality (concerning follow up beyond induction) and infectious or cardiovascular adverse events (during induction treatment).

Data on potential confounding factors, as the possibility of enrollment of specific prognostic subgroups of AML patients (such as secondary AML patients, either therapy-related or as a disease progression from myelodysplastic syndrome/myeloproliferative neoplasm or acute promyelocytic leukaemia patients) and individual cytogenetic prognostic risk data, was also collected.

Considering the recommendations by The Cochrane Collaboration [15] group and taking into account additional study characteristics, we assessed methodological quality and risk of bias of all included RCTs, which were independently examined by two investigators in duplicate (including always two reviewers amongst authors L. S., V. D. M. and K. M. L) for the adequacy of the following characteristics: allocation concealment; sample size calculation; blinding of participants, personnel and outcome assessors; incomplete outcome data; intention to treat analysis; and selective reporting bias. When articles provided insufficient data to evaluate any of these parameters, and no information was retrieved from contact with authors, they were classified as unclear.

Data synthesis and analysis

We chose to perform compilation of evidence through a MTC, which merges direct and indirect comparisons concomitantly into unique point estimates and variances [16]. Depending on the complexity and completeness of the network resultant from multiple trials, it can originate narrower interval estimates. These models are supported by the Bayesian hierarchical framework and are greatly versatile, allowing data from more than two arms trials and heterogeneous between-trials variability. In this study, the CDD was considered the baseline treatment. The goodness of fit of the models was evaluated by means of residual deviance and deviance information criteria. MTC analyses were carried out considering both fixed and random effect models. Consistency assumption was assessed through posterior plots and the Bayesian p-values produced by the node-splitting method described by Dias et al. [17]; significance level was set to 0.02, in order to adjust for multiple comparisons. MTC were carried out in the software WINBUGS version 1.4.3 (MRC Biostatistics Unit, Cambridge, UK).

Results

Search results and characteristics of included studies

A total of 3613 references were retrieved from electronic databases searches: 1159 from MEDLINE, 2100 from EMBASE, 323 from Cochrane CENTRAL, 12 from Scielo and 19 from LILACS. No other relevant study was found whilst searching through reference lists of included studies and previous systematic reviews. Eventually, 17 RCTs were considered eligible for meta-analysis. The study flowchart, as proposed in PRISMA statement [11], is shown in Figure 1.

We identified 12 RCTs comparing CDD and IDA, 3 comparing CDD and HDD and 2 comparing IDA and HDD. A list of studies from each respective comparison is shown in Table 2, with population data and treatment schedules. The network of evidence is displayed in Figure 2.

Methodological quality of included studies was rather low. None of the studies described blinding of patients, outcomes assessors, caregivers or statisticians [18–34]. Only two trials described allocation concealment of treatments [26,28]. Moreover, only seven studies followed an intention-to-treat analysis [22,24,26,28,29,33,34]. Details on methodological quality assessment and risk of bias can be found in Table 3.
Descriptive analysis of pooled data

Altogether, 7258 patients could be evaluated. A total of 4873 CR (67.1%) were observed. For those who attained CR, 79.5% did so after the first cycle of chemotherapy. For those trials that reported deaths by the end of induction, there was a mean of 11.0% of induction-related mortality. For those studies reporting data on long-term follow up, a mean overall mortality of 67.6% was observed.

Complete remission and mortality outcomes

The primary outcome evaluated was CR (Figure 3). We found that IDA showed higher rates of CR when compared with CDD [relative risk (RR) 1.13, 95% credible interval (CrI) 1.05–1.23]. A similar result could be observed for HDD confronted with CDD (RR 1.13, 95% CrI 1.02–1.26). However, no difference was observed when IDA and HDD were compared against each other (RR 1.00, 95% CrI).
0.89–1.11). Direct and indirect comparisons showed consistency in results ($p > 0.02$ in all node-splitting evaluations).

On the basis of reported results of 13 studies [18, 20–25, 28–30, 32–34], when considering only those patients that attained FC-CR (given that all studies allowed reinduction at least once for patients showing resistant disease after the first cycle before considering it as induction failure) it was shown that both IDA (RR 1.37, 95% CrI 1.22–1.54) and HDD (RR 1.32, 95% CrI 1.18–1.50) demonstrated higher FC-CR rates than CDD. Again, HDD and IDA showed no significant differences in FC-CR rates (RR 0.97, 95% CrI 0.86–1.10) when compared with each other. Evidence was consistent through direct and indirect comparisons ($p > 0.02$).

**Figure 2.** Network of evidence for mixed treatment comparison meta-analysis. Numbers identify the quantity of randomized clinical trials eligible for each direct comparison.

**Table 3.** Methodological quality and risk of bias of included randomized clinical trials

<table>
<thead>
<tr>
<th>Study</th>
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<th>Sample size calculation</th>
<th>Blinding of participants and personnel</th>
<th>Blinding of outcome assessors</th>
<th>Incomplete outcome data</th>
<th>Intention to treat analysis</th>
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**Figure 3.** Mixed treatment comparison analysis for complete remission, induction mortality and long-term overall mortality.
Because of insufficient data, we were not able to extract isolated information that referred to induction mortality in 5 of 17 studies included in this analysis [19,23,24,27,31]. Information on overall mortality could not be extracted from long-term follow up in 4 of 17 studies [19,22,26,29]. There was no difference in induction mortality (Figure 3) between IDA and CDD (RR 1.15, 95% CrI 0.81–1.53), HDD and CDD (RR 0.90, 95% CrI 0.90–0.95) and HDD and IDA (RR 0.90, 95% CrI 0.90–0.95). However, concerning long-term overall mortality (Figure 3), IDA showed significant lower mortality compared with CDD (RR 0.93, 95% CrI 0.86–0.99) and was found no different from HDD (RR 1.01, 95% CrI 0.91–1.11). Also, HDD did not show a significant difference in overall mortality rate when compared with CDD (RR 0.94, 95% CrI 0.85–1.02). Evidence on both mortality outcomes was also consistent throughout comparisons (p > 0.02).

Adverse events

Infectious events during induction were not more frequent when IDA and CDD (RR 0.98, 95% CrI 0.91–1.08), HDD and CDD (RR 1.00, 95% CrI 0.93–1.09) and HDD and IDA (RR 1.03, 95% CrI 0.92–1.12) were compared. Similar results were seen when cardiotoxicity was compared between IDA and CDD (RR 1.12, 95% CrI 0.62–2.05), HDD and CDD (RR 0.84, 0.30–1.81) and HDD and IDA (RR 0.76, 95% CrI 0.25–1.69). All comparisons were also consistent in these outcomes (p > 0.02).

Discussion

In this systematic review, we gathered all available evidence published so far comparing three AML induction regimens: CDD, HDD and IDA. Both HDD and IDA showed 13% of improvement in CR rates when compared with CDD. When confronted with each other, however, both treatment regimens seemed equally effective in CR and FC-CR. Increase in CR rates was not accompanied by toxicity augmentation, as one would expect. The incidence of adverse events, namely, cardiotoxicity and infectious events, were comparable amongst all treatment groups. Likewise, mortality related to induction treatment was not increased with IDA or HDD. Notwithstanding their superior response rates, only IDA showed lower rates of mortality in the long term when compared with CDD, whereas HDD failed to show benefit over CDD. This latter finding, however, needs support from further studies, as the amount of evidence included in this comparison is probably underpowered.

The AML Collaborative Group analysed five induction trials of IDA and CDD in an individual patient data meta-analysis, finding a better CR rate and OS for IDA [10]. Dose intensification of anthracyclines was not yet investigated by that time. More than a decade later, Ziogas et al. undertook a compilation of direct and indirect evidence, similar to our study, concerning induction of elderly patients [1]. It was a network meta-analysis including 65 randomized trials on patients older than 60 years that concluded that although two IDA-containing treatment approaches could possibly result in higher CR rates, this was not translated into survival benefit, in opposition to the preceding study. A remark that should be made regarding Ziogas study is that the compilation of only poor prognostic patients (as is the case for older patients) could have blunted drug-specific efficacy. Teuffel et al. studied the population younger than 60 years (including children) in a conventional meta-analysis of induction approaches [6]. In this study, data on a paediatric and adult population was, to our knowledge, inadvertently combined, because children tend to show markedly higher CR and survival rates than adult patients [35,36]. HDD (which was included in a meta-analysis for the first time), and IDA showed higher CR rates than CDD, but an HDD and IDA comparison was not included in the study, not allowing the appraisal of which of these treatments was superior. Also, it was found that HDD could result in a lower overall mortality than CDD, differing from our findings. However, it should be emphasized that, in this meta-analysis, the classic study by Yates et al. [37] had its 45 mg/m² dose arm classified as HDD, which is not accurate according to current practice. More recently, Wang published a conventional meta-analysis comparing IDA and DNR regardless of schedule. It was found that IDA was superior to DNR in CR and OS. In a dosage stratified subanalysis, it was shown that this benefit was seen only when IDA was compared with CDD, whereas no difference resulted when confronted with HDD. Therefore, IDA and HDD superiority in CR induction can be considered consistently supported in medical literature, as in our findings. Nevertheless, an important contribution from the results in the present study is that IDA and HDD seem effectively comparable in terms of antineoplastic activity, whilst implying no significant difference in treatment-related toxicity when compared with standard treatment.

On the basis of our results, it is possible to consider that IDA superiority over DNR could be a matter of cytotoxic dose equivalence between different drugs rather than a drug-specific effect. Increasing the dose of DNR seems to lead to the same results attained with IDA, with no excess of immediate toxicity. However, one must remember that cardiac side effects from anthracycline use are seldom detected in the short-term follow up, implying that, for an accurate analysis of inherent therapy-related toxicity, long-term side effects should also be accounted for.

Our findings on overall mortality support superiority of IDA in the long-term follow up when compared with...
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CDD. This finding supports that from Wheatley et al. [10] study, where this trend on mortality was first observed in a meta-analysis. On the other hand, although HDD was no different from IDA in overall mortality, it did not show benefit over CDD in this outcome, contradicting findings from Teuffel et al. [8]. It is possible, however, that the data concerning HDD trials [21,23,24,28,29] is still scarce to show consistent differences. Moreover, HDD studies are relatively new (beginning in 2009) and have shorter follow up periods than CDD and IDA trials, possibly underestimating long-term effect on survival. It should also be noted that DNR, even in higher doses protocols, results in lower costs than IDA-containing schemes of therapy. Results on long-term mortality for IDA should be examined carefully. We reviewed studies with heterogeneous follow up periods. Mortality rates are expected to increase over a period because of disease relapse, progression or treatment-related mortality, and effect of therapy could have been influenced by variable follow up trials. Another important drawback in compiling data on this outcome is that there is also heterogeneity in postremission therapy (e.g. consolidation, maintenance and allogeneic and autologous bone marrow transplantation referral) throughout trials. These differences possibly influence the chance of relapse for those in CR and eventually mortality.

Idarubicin and HDD are unequivocally better choices of treatment than CDD when CR induction is concerned, with no apparent additional toxicity burden in the short term. Aside from resulting in higher CR rates than CDD, IDA also showed a modest benefit in long-term overall mortality. On the other hand, HDD advantage in CR was not translated into superior survival results when compared with CDD in the present study. On the basis of these remarks, we believe that there is no longer a reason to maintain CDD as a standard treatment approach for adult AML patients. Intensifying dose of DNR or changing it to IDA consistently lead to a more effective control of disease and can possibly imply higher rates of overall long-term survival. Focus should be kept on developing and providing adequate supportive care to allow responsive patients to maintain their response and survive through therapy-related toxicity.

Conflict of interest

The authors have no competing interest.

Ethics statement

This research has been approved by the ethics committee of our institution and is in accordance with the statements of the Declaration of Helsinki.

References