Chapter

What Is the Best Choice and Dose of Anthracycline for Induction Chemotherapy in Acute Myeloid Leukemia?

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Abstract

Treatment of patients with acute myeloid leukemia, medically fit to receive intensive chemotherapy, has been standardized over the past four decades and consists of an anthracycline administered along with continuous cytarabine. This combination is traditionally administered as seven days of cytarabine and three days of anthracycline, known as 7 + 3. Selecting the appropriate choice and dose of anthracycline for induction chemotherapy continues to be debated. Daunorubicin, used in three doses of either 45 mg/m^2, 60 mg/m^2 or 90 mg/m^2, and idarubicin 12 mg/m^2 are the two commonly used anthracyclines in clinical practice. Other anthracyclines including mitoxantrone and liposomal daunorubicin are incorporated in the treatment algorithm as well. Our understanding of the underlying biology of acute myeloid leukemia has significantly increased in the past decade, helping us formulate individualized treatment plans. In this chapter, we will discuss pivotal studies comparing the safety and efficacy of different types and doses of anthracyclines, focusing predominantly on daunorubicin and idarubicin. The details of the study design as well as subgroup analysis will be presented to determine which subset of patients with AML may benefit from a particular anthracycline.

Keywords: AML, induction chemotherapy, anthracycline, daunorubicin, Idarubicin

1. Introduction

Acute Myeloid Leukemia (AML) is a heterogenous clonal stem cell disorder, resulting in proliferation of immature hematopoietic cells in the bone marrow, peripheral blood and occasionally in other tissues. Consequentially, normal hematopoiesis is inhibited, resulting in neutropenia, anemia and thrombocytopenia. Patients usually present with signs and symptoms of underlying bone marrow failure including fatigue, lethargy, shortness of breath, bruising, bleeding and infections [1–3].

The incidence rate of AML increases progressively with advancing age. It is primarily a disease of the elderly with the median age at diagnosis being 68 years and accounts for 80–90% of all acute leukemias in adults. There are approximately 20,000 new cases of AML diagnosed every year in the United States, accompanied by nearly 10,000 deaths [1, 3, 4].

Our understanding of the molecular pathogenesis of AML has increased significantly in the last decade. Unfortunately, this understanding has not been matched in terms of therapeutic advances, though this has slowly changed since 2017. Age, cytogenetics and molecular aberrations play a significant role in determining prognosis as well as choice of treatment in patients with AML [2, 5, 6].

Treatment of AML can broadly be divided into intensive and non-intensive chemotherapy. Currently, in addition to age, performance status and medical fitness influence intensity of treatment. Traditionally, young and medically fit patients are treated with an intensive chemotherapy regimen. An arbitrary cutoff of 55 to 65 years has commonly been used to define 'older' and 'younger' patients. Medical fitness can be determined relatively accurately by assessing variables including performance status, organ function and frailty. A combination of age and medical fitness routinely form the basis for the assignment to the intensity of treatment [7–12].

Intensive chemotherapy generally involves a remission induction phase, to achieve complete remission, followed by a post-remission or consolidation phase, to stay in remission and prevent relapse. A combination of an anthracycline and cytarabine is almost always used as upfront intensive therapy for patients with AML. Nearly four decades ago, 7 days of cytarabine and 3 days of daunorubicin was established as the standard of care for patients with AML. Even today, this regimen, commonly known as 7 + 3, serves as the backbone in the treatment algorithm for AML. Since the 1970s, many trials have attempted to improve upon this combination either by using different doses of anthracyclines, different types of anthracyclines or adding a third agent. With very few exceptions, 7 + 3 remains standard of care outside of clinical trials [13, 14].

To this day, it is not entirely clear which type and dose of anthracycline is ideal when used during induction chemotherapy. Daunorubicin and idarubicin have been compared extensively in randomized studies. Mitoxantrone is also considered at times. CPX-351 (liposomal daunorubicin:cytarabine) is FDA approved, as induction therapy, in a subset of patients with AML.

In this chapter, we will present the data comparing the different types and doses of anthracyclines used in induction chemotherapy. Whereas details on all agents will be provided, the main focus will revolve around daunorubicin (45 mg/m^2, 60 mg/m^2 and 90 mg/m^2) and idarubicin (mainly 12 mg/m^2) since they are the most commonly used anthracyclines. Furthermore, randomized studies where induction chemotherapy was not given in a 7 + 3 manner have also been discussed.

2. Daunorubicin

Daunorubicin, a topoisomerase II inhibitor, inhibits both DNA and RNA synthesis by intercalating between DNA base pairs, inhibiting transcription by inhibiting DNA-dependent RNA polymerase as well as steric obstruction. It was discovered as an antitumor antibiotic in the 1960s and has since been used as part of the treatment algorithm for AML [15]. In 1973, Yates et al. shared their findings of using 7 days of continuous cytarabine infusion and 3 days of daunorubicin in patients with AML. They reported a complete remission rate of 63% in 8 untreated patients with AML. The superiority of this regimen was confirmed by CALGB 7421, a trial comparing 7 + 3 to 5 days of continuous cytarabine infusion and 2 days of anthracycline (5 + 2) [13, 14]. Thus, 7 + 3 became the backbone of AML treatment for the next four decades and remains the standard to which other therapies are compared to even today.

The dose of daunorubicin used by Yates et al. as well as CALGB 7421 was 45 mg/m^2 and this dose was used as standard going forward after confirmatory results of CALGB 7721. Since then, several attempts have been made to modify the dose of daunorubicin, as part of standard induction therapy, to further improve outcomes of patients with AML [6, 16–19].

2.1 Daunorubicin 45 mg/m^2 vs. 90 mg/m^2

2.1.1 Older adults

A HOVON-SAKK-AMLSG collaboration investigated escalated daunorubicin dose (90 mg/m^2) vs. standard daunorubicin dose (45 mg/m^2) with 200 mg/m^2 of cytarabine continuous infusion (7 + 3) in older adults with AML [20]. The study enrolled 813 patients with a median follow-up of 40 months. The median age of the study population was 67 years (range 60–83). Around 60% of the study population had intermediate-risk cytogenetics. All patients received a second cycle of cytarabine at a dose of 1000 mg/m^2, every 12 hours, for 6 days.

The escalated dose was associated with higher rates of complete remission when compared to standard dose (64% vs. 54%, $p = 0.002$) as well as higher rates of complete remission after first cycle of induction (52% vs. 35%, $p < 0.001$). There were no significant differences in terms of toxicities and early mortality between the 2 doses. For the overall population, there was no difference in overall survival, event-free survival and disease-free survival between the 2 doses. In a subset analysis of patients between the ages of 60 and 65, the escalated dose was associated with higher rates of complete remission, event-free survival (29% vs. 14%) and overall survival (38% vs. 23%). Within the limitations of the small numbers, older patients with core-binding factors abnormalities also seemed to derive survival benefit with the escalated dose.

2.1.2 Younger adults

In ECOG 1900, Fernandez et al. investigated 3 days of high dose daunorubicin at 90 mg/m^2 vs. standard dose daunorubicin at 45 mg/m^2, in combination with 100 mg/m^2 of cytarabine as continuous infusion (7 + 3), in young patients with AML [21]. The study enrolled 657 patients with a median age of 48 years (range 17–60). A second round of induction was given to patients with residual disease on day 14 bone marrow biopsy. The regimen was 7 + 3 with a daunorubicin dose of 45 mg/m^2. Approximately 41% of the patients had intermediate-risk cytogenetics and 14% and 19% had favorable and unfavorable-risk cytogenetics, respectively.

The rates of complete remission were higher with high dose daunorubicin compared to standard dose (70.6% vs. 57.3%, $p < 0.001$). The rates of complete remission after first induction were also higher in the high dose arm (83.3% vs. 72%). There was no difference in early mortality between the 2 doses. High dose daunorubicin was associated with a higher 4-year overall survival (39% vs. 31%, $p = 0.001$), median overall survival (25.4 m vs. 16.6 m, $p = 0.001$) and event-free survival (28% vs. 20%, $p < 0.001$). Subgroup analysis demonstrated that patients younger than 50 years benefit significantly with high dose daunorubicin with higher complete remission rates (74.3% vs. 59.4%) and improved survival (median overall survival: 34.3 m vs. 19.0 m, HR 0.65, $p = 0.004$). The benefit of high dose daunorubicin did not extend to patients ≥50 years.

Survival with high dose daunorubicin was numerically longer, but statistically insignificant, in patients with favorable-risk cytogenetics, when compared to

standard dose. Patients with intermediate-risk cytogenetics benefitted from high dose daunorubicin, compared to standard dose, with a median overall survival of 32.3 m vs. 17.8 m (HR 0.67, p = 0.02). There was no difference in survival between the 2 doses for patients with unfavorable cytogenetics as well as those with FLT3-ITD or MLL-PTD mutations.

An updated report of ECOG 1900 was presented in 2016 with a longer follow-up time period (median 80.1 months amongst survivors) [22]. The update confirmed the benefit of high dose daunorubicin in patients younger than 50 years of age (44.7 m vs. 20.7 m, 9 = 0.002). Older patients did not gain survival advantage with the high dose.

The benefit of high dose daunorubicin, compared to standard dose, was shown in patients with both favorable (NR vs. 39.4 m, HR 0.51, p = 0.03) and intermediate-risk cytogenetics (33.5 m vs. 20.1 m, HR 0.68, p = 0.01). After controlling for confounding variables, a benefit for patients with unfavorable-risk cytogenetics was also seen with the high dose (HR 0.66, p = 0.04).

Subset analysis based on molecular subgroups revealed that FLT3-ITD, DNMT3A and NPM1 mutant-AML derived benefit from high dose daunorubicin. Patients with FLT3-ITD mutated AML had a 4-year overall survival of 28% with high dose daunorubicin compared to 17% with standard dose. The data suggests that an additional 10% of patients with FLT3-ITD mutated AML can be cured with the higher dose. Further analysis demonstrated that both younger and older patients with FLT3-ITD mutant AML derived benefit from high dose daunorubicin. Patients with DNMT3A mutant AML had longer median overall survival with high dose daunorubicin, compared to standard dose (16.5 m vs. 14.1 m). However, the benefit of high dose daunorubicin, in DNMT3A mutant AML, was limited to patients younger than 50 years of age. Both younger and older patients with NPM1 mutant AML derived benefit with high dose daunorubicin. The median overall survival with high dose daunorubicin was 75.9 months, compared to 16.9 months with standard dose. The 4-year overall survival increased with high dose daunorubicin to 52% from 29% with standard dose.

Another phase III study compared high dose daunorubicin at 90 mg/m^2 for 3 days with standard dose daunorubicin at 45 mg/m^2 for 3 days, in addition to cytarabine 200 mg/m^2 as continuous infusion, in adults ≤60 years of age with AML [23]. The study enrolled 383 patients. A second round of abbreviated induction was given to patients with residual disease on day 14 bone marrow biopsy. Approximately 62% of the patients had intermediate-risk cytogenetics and 21% and 15% had favorable and unfavorable-risk cytogenetics, respectively.

The rates of complete remission were higher with daunorubicin 90 mg/m^2 when compared to 45 mg/m^2 (82.5% vs. 72.0%, p = 0.014). After a median follow-up of 52.6 months, high dose daunorubicin, compared to standard dose, was associated with improved overall survival (46.8% vs. 34.6%, p = 0.03) and event-free survival (40.8% vs. 28.4%, p = 0.03). There was no difference in the toxicity profile in both arms. In multivariable analysis, high dose daunorubicin was associated with higher complete remission rate (HR, 1.802, P = 0.024), improved overall survival (HR, 0.739, P = 0.032) and event-free survival (HR, 0.774, P = 0.04). Based on cytogenetic risk group, the benefit was of high dose daunorubicin was mainly seen in patients with intermediate risk disease. Molecular subgroup analysis was not available.

2.2 Daunorubicin 45 mg/m^2 vs. 60 mg/m^2

There is no randomized data comparing daunorubicin 60 mg/m^2 to daunorubicin 45 mg/m^2. One retrospective study evaluated 56 patients and reported

complete remission rates of 88% with daunorubicin 60 mg/m^2 and 67% with daunorubicin 45 mg/m^2 (p = 0.05). Details on disease-free and overall survival were not available [24].

2.3 Daunorubicin 60 mg/m^2 vs. 90 mg/m^2

The UK NCRI AML17 trial compared daunorubicin 60 mg/m^2 to 90 mg/m^2 in AML induction [25]. The induction chemotherapy regimen was not administered as standard 7 + 3 and used a modified strategy of giving the anthracycline on days 1, 3 and 5, in combination with cytarabine 100 mg/m^2, every 12 hours, on days 1 to 10. Furthermore, a second round of induction was given to all patients in morphological remission after the first induction and consisted of daunorubicin 50 mg/m^2 on days 1, 3 and 5 and cytarabine 100 mg/m^2, every 12 hours, on days 1–8. Hence the cumulative dose of daunorubicin in the 90 mg/m^2 and 60 mg/m^2 arms was 420 mg/m^2 and 330 mg/m^2, respectively. The cumulative dose for both doses, if used in a 7 + 3 regimen, would have been 270 mg/m^2 and 180 mg/m^2, respectively.

The study enrolled 1206 patients with a median age of 53 years (range 16–72 years). Nearly three fourths of the patients in the study had intermediate risk cytogenetics. After a median follow-up of 14.8 months, the study was terminated prematurely due to higher risk of mortality by day 60 in the daunorubicin 90 mg/m^2 arm, with an intention-to-treat analysis showing no benefit of the higher dose. There was no difference in the rate of complete remission between the 2 arms (D60 75% vs. D90 73%, p = 0.6). There was no difference in 30-day mortality between the 2 arms, but 60-day mortality was higher with daunorubicin 90 mg/m^2, compared to 60 mg/m^2 (10% vs. 5%, p = 0.001). Furthermore, there was no statistical difference between the 2 arms in terms of overall survival (D60 60% vs. D90 59%, p = 0.15), relapse-free survival (D60 48% vs., D90 51%, p = 0.7) and 2-year overall survival censored at stem cell transplant (D60 60% vs. D90 60%). An exploratory analysis did not identify any subgroup that benefited with the higher dose of daunorubicin.

An updated intention-to-treat analysis, after a median follow-up of 28 months, revealed no differences in terms of rates of complete remission, overall survival, and relapse-free survival [26]. However, subgroup analysis indicated that the higher dose of daunorubicin may benefit patients with FLT3-ITD mutant AML, (Cumulative incidence of relapse: 44% vs. 60%; HR, 0.58; p = .01; RFS: 45% vs. 33%; HR, 0.63; p = .02; OS: 54% vs. 34%; HR, 0.65; p = .03). The survival benefit seemed to be independent of the allelic burden of the mutation as well as coexisting NPM1 mutations.

Data from the DaunoDouble trial were recently presented at the European Hematology Association in the form on an abstract [27]. The trial compared daunorubicin 60 mg/m^2 to daunorubicin 90 mg/m^2 when given as 7 + 3. Daunorubicin was given on days 3 to 5. The study enrolled 262 patients and the median age of the population was 52 years. Per the European Leukemia Network 2017 classification, there were 39% patients with favorable, 40% with intermediate and 21% with adverse risk disease. Response assessment was based on a day 15 bone marrow and patients with <5% blasts were further randomized to either receive a second induction with 7 + 3 or to no further induction. The results of the second randomization are not yet available. The rate of remission with a maximum of two rounds of induction was 67% with daunorubicin 60 mg/m^2 and 61% with daunorubicin 90 mg/m^2 (p = 0.32). With a median follow-up of 40 months, there was no difference in cumulative incidence of relapse (p = 0.343) and treatment related mortality (p = 0.994). There was no difference in 4-year overall survival (p = 0.108), event-free survival (p = 0.207) and relapse-free survival (0.394) between the 2 groups and

Study	Patients (n)	Age (median, range)	Anthracycline comparison	Induction schedule	Cumulative anthracycline dose (mg/m^2)	Complete remission	Overall survival	Subset analysis
HOVON-SAKK-AMLSG	813	67 (60–83)	D90 vs. D45	7 + 3	D90 270 D45 130	Favors D90	No significant difference	60–65 years: CR, EFS and OS improved with D90
ECOG 1900	657	48 (17–60)	D90 vs. D45	7 + 3	D90 270 D45 130	Favors D90	Favors D90	Cytogenetics: All risk groups had improved OS with D90 FLT3: Improved OS with D90 NPM1 Improved OS with D90 DNMT3A & <50 years: Improved OS with D90
Lee et al.	383	N/A (15–60)	D90 vs. D45	7 + 3	D90 270 D45 130	Favors D90	Favors D90	Cytogenetics: Intermediate risk had improved OS with D90
UK NCRI AML17	1206	53 (16–72)	D90 vs. D60	10 + 3	D90 420 D60 330	No significant difference	No significant difference	FLT3: May benefit from D90
Daunodouble	262	52 (N/A)	D90 vs. D60	7 + 3	D90 270 D60 180	No significant difference	No significant difference	Complete data not available

D90: daunorubicin 90 mg/m^2, D60: daunorubicin 60 mg/m^2, D45: daunorubicin 45 mg/m^2, 7 + 3: 7 days of cytarabine and 3 days of anthracycline, CR: complete remission, EFS: event-free survival, OS: overall survival.

Table 1.
Summary of trials comparing different doses of daunorubicin.

there was no difference in outcomes based on daunorubicin dose on multivariable analysis. Although these results support the use of daunorubicin 60 mg/m^2, results from the second randomization in the study will facilitate with data interpretation.

A summary of the trials comparing different doses of daunorubicin is presented in **Table 1.**

2.4 FLT3-mutant AML

A randomized study compared the addition of midostaurin, a multitarget kinase inhibitor, or placebo to 7 + 3 in FLT3 mutated AML. The dose of daunorubicin was 60 mg/m^2 and patients were < 60 years of age. Compared to placebo, the addition of midostaurin prolonged overall and event-free survival in this population [18]. Whether using daunorubicin 90 mg/m^2 or idarubicin would have yielded even better results remain unknow. There is data (discussed below) that daunorubicin 90 mg/m^2 may be the optimal choice to use in FLT3 mutated AML.

3. Idarubicin

3.1 Idarubicin 12 mg/m^2 vs. daunorubicin 45 mg/m^2

Idarubicin was introduced into the treatment of AML, as a newer anthracycline, in the 1990s. Four trials during that time compared idarubicin 12–13 mg/m^2 for 3 days to daunorubicin 45–50 mg/m^2 for 3 days, given with cytarabine as induction chemotherapy for AML. Three of those studies found idarubicin to be superior to daunorubicin and there was a signal of rapid response to idarubicin, compared to daunorubicin, in the fourth study [28–31]. Another study compared daunorubicin 50 mg/m^2 for 3 days to idarubicin 8 mg/m^2 for 5 days, given with seven days of cytarabine, and found idarubicin to be more effective than daunorubicin in AML patients between 55 and 75 years of age [32]. In summary, idarubicin at an average dose of 12 mg/m^2 is most likely superior to daunorubicin 45 mg/m^2, when administered with cytarabine as induction chemotherapy.

3.2 Idarubicin vs. high dose daunorubicin

3.2.1 Idarubicin 12 mg/m^2 vs. daunorubicin 90 mg/m^2

Since idarubicin was found to be superior to standard dose daunorubicin (45 mg/m^2), the next obvious comparison was between idarubicin and high dose daunorubicin. Studies that compare idarubicin to dose intensified daunorubicin delivered as either higher daily doses or prolonged administration of the standard dose have been conducted. In general, regimens with dose intensified daunorubicin have targeted to achieve a cumulative dose of 240–280 mg/m^2 during induction. Key prospective randomized studies comparing these strategies are summarized here.

A Phase III randomized, noninferiority study conducted in South Korea was reported in 2017 [33]. There were 299 patients with a median age of 49 years (range 15–65). They were randomized to receive infusional cytarabine 200 mg/m^2 for 7 days with either idarubicin 12 mg/m^2 or daunorubicin 90 mg/m^2 for 3 days. If Day 14 bone marrow assessment revealed persistent disease, patients received an additional round of induction with infusional cytarabine for 5 days plus idarubicin 8 mg/m^2 or daunorubicin 45 mg/m^2. Patients received consolidation therapy followed by transplantation (either allogeneic or autologous) in first remission based on their cytogenetic risk stratification and donor availability. There was a higher proportion

of secondary (4.7% vs. 11.3%), poor risk (14.5% vs. 27.5%) and good risk (18.6% vs. 23.5%) disease in the daunorubicin arm, while more intermediate risk disease (66.9% vs. 49%) was present in the idarubicin arm. These differences did not have significant impact on outcomes. Other baseline characteristics as well as post remission therapies received were similar between the two treatment arms.

In this study, rates of complete remission (80.5% v 74.7%; P = .224), 4-year overall survival (51.1% vs. 54.7%, p = 0.756), cumulative incidence of relapse (35.2% v 25.1%; P = .194) and event-free survival (45.5% v 50.8%; p = 0.772) did not differ between the idarubicin and daunorubicin arms, respectively. However, in the subgroup analysis of FLT3-ITD-mutant AML (n = 44; idarubicin n = 27; daunorubicin n = 17) the median overall survival (not reached vs. 15.2 m, p = 0.03) and event-free survival (not reached vs. 11.9 m, p = 0.03) favored the daunorubicin arm, while remission rates were similar (88.2% vs. 74.1%) in both groups. No differences were noted in the non FLT3-ITD-mutant subgroup. Adverse events were similar between both groups.

In summary, this study showed noninferiority of high dose daunorubicin compared to standard dose idarubicin. There is a suggestion that high dose daunorubicin improved survival, but not remission rate, in FLT3-ITD-mutant AML. However, the study was not powered adequately to draw definitive conclusions in this subgroup analysis.

3.2.2 Idarubicin 12 mg/m^2 vs. daunorubicin 50 mg/m^2 (over 5 days)

The JASLG AML 201 phase III randomized, noninferiority study compared standard dose idarubicin to high dose daunorubicin defined as 50 mg/m^2 over 5 days (as opposed to 90 mg/m^2 over 3 days) [34]. This study had a second phase of randomization for consolidation therapy after complete remission was attained. There were 1057 patients, with a median age of 47 years (range 14–65), randomized in the first phase to receive infusional cytarabine 100 mg/m^2 for 7 days plus idarubicin or daunorubicin at the above-mentioned doses. Baseline characteristics were well balanced between the two groups. In this study, overall complete remission rate was 77.9% and did not differ between the idarubicin (78.2%) and daunorubicin (77.5%) arms, establishing non-inferiority of high dose daunorubicin. Furthermore, 64.1% vs. 61.1% of patients achieved a CR after the first round of induction in the idarubicin and daunorubicin arms, respectively. There was no difference in overall and relapse-free survival between the 2 arms.

3.2.3 Idarubicin 12 mg/m^2 vs. daunorubicin 80 mg/m^2

ALFA 9801, a randomized study, compared daunorubicin 80 mg/m^2 for 3 days to standard dose idarubicin 12 mg/m^2 (IDA3) in patients aged 50–70 years. A third arm of idarubicin 12 mg/m^2 for 4 days (IDA4) was also added [35]. Patients who had residual disease on a day 20 bone marrow assessment could receive additional induction with a pre-specified mitoxantrone based regimen. Those who achieved complete remission then received 2 cycles of consolidation with intermediate dose cytarabine + anthracycline based on their randomization group. This study had a second phase of randomization which investigated the role of recombinant IL-2 in maintenance therapy, which will not be discussed in this chapter. Four hundred and seventy-eight patients underwent the first phase of randomization and baseline characteristics were well balanced in the three arms. Overall complete remission rate was found to be lower in the daunorubicin arm (70%) compared to the IDA3 (83%) or IDA4 (78%) arms and this difference was statistically significant. However, there was no difference in remission rates after the first induction therapy.

No significant difference was noted in the secondary outcomes of event-free survival, overall survival, and cumulative incidence of relapse between the three arms. Induction related deaths, cytopenias and duration of hospitalization was also similar between the groups. Thus, in this older population of AML patients, while the overall complete remission rates appear to be higher in the idarubicin group, no differences were noted in remission after first induction, overall survival or event-free survival.

3.2.4 Idarubicin 8 mg/m^2 (5 days) vs. daunorubicin 60 mg/m^2

Another trial comparing idarubicin to high dose daunorubicin based induction was the phase III GOELAMS LAM-2001 trial, which included patients between the ages of 17–60 years [36]. The study was primarily designed to compare single vs. tandem autologous hematopoietic stem cell transplant strategies as post remission therapy, however the initial phase randomized 832 patients to receive either idarubicin or daunorubicin based induction. The induction regimen used here was infusional cytarabine 200 mg/m^2 for 7 days plus either idarubicin 8 mg/m^2 for 5 days (cumulative dose of 40 mg/m^2 during induction) or daunorubicin 60 mg/m^2 for 3 days. This study revealed similar complete remission rates between the two groups (83% vs. 81%). Seven-year long term follow up of the patients randomized in the first phase of the study was reported in 2013, looking at a variety of cox proportional models to account for interactions with the second randomization arm. Patients in the idarubicin arm had an improved 7-year OS, compared to daunorubicin, unless they had unfavorable cytogenetics. A subset analysis of patients with intermediate risk cytogenetics (n = 393) demonstrated improved 7-year overall survival (p = 0.005) as well as event-free survival (p = 0.025) with idarubicin [37].

3.2.5 Idarubicin 9 mg/m^2 (4 days) vs. daunorubicin 45 mg/m^2 (4 days)

ALFA 9803 was designed to compare two different post-remission strategies but included a first phase of randomization comparing idarubicin to daunorubicin. There were 416 patients aged 65 years or older, randomized to receive infusional cytarabine for 7 days, with either daunorubicin 45 mg/m^2 for 4 days (cumulative dose 180 mg/m^2) or idarubicin 9 mg/m^2 for 4 days (36 mg/m^2). There was no difference in complete remission rates or toxicity profiles between the two induction strategies [38].

Finally, combined long term outcomes of patients enrolled in the ALFA 9801 and 9803 studies have been reported to identify factors associated with improved long-term survival. This report interestingly revealed randomization to idarubicin to be associated with an improved cure rate (16.6% vs. 9.8%), although standard survival analysis in the independent trials did not reveal any differences between idarubicin and daunorubicin based induction [39].

3.2.6 Idarubicin 12 mg/m^2 vs. daunorubicin 60 mg/m^2

There is no randomized or retrospective data comparing idarubicin 12 mg/m^2 to daunorubicin 60 mg/m^2, when administered with continuous cytarabine as 7 + 3. Both these doses are frequently used interchangeably in clinical trials but whether their efficacy is equivalent is not well defined.

Two meta-analysis compared the efficacy of idarubicin to daunorubicin. One focused on high dose daunorubicin only and found that idarubicin was associated with higher rates of complete remission and lower rates of refractory disease compared to daunorubicin. There was no difference in early mortality, febrile

Study	Patients (n)	Age (range)	Anthracycline comparison	Induction schedule	Cumulative anthracycline dose (mg/m2)	Complete remission	Overall survival	Subset analysis
NCT01145846	299	49 (15–65)	D90 vs. Ida12	7 + 3	D90 270 Ida 36	No significant difference	No significant difference	FLT3: Improved OS and EFS with D90
JASLG AML 201	1057	47 (14–65)	D50 vs. Ida12	7 + 3 (Ida) 7 + 5 (D50)	D50 250 Ida 36	No significant difference	No significant difference	—
ALFA 9801	468	60 (50–70)	D80 vs. Ida12	7 + 3	D80 240 Ida 36	Favors Ida	No significant difference	—
GOELAMS LAM-2001	832	48 (17–60)	D60 vs. Ida8	7 + 3 (D60) 7 + 5 (Ida)	D60 180 Ida 40	No significant difference	Favors Ida	Cytogenetics: Intermediate risk had improved OS and EFS with Ida
ALFA 9803	416	72 (65–85)	D45 vs. Ida9	7 + 4	D45 180 Ida 36	No significant difference	No significant difference	—

D90: daunorubicin 90 mg/m^2, D80: daunorubicin 80 mg/m^2, D60: daunorubicin 60 mg/m^2, D50: daunorubicin 50 mg/m^2, D45: daunorubicin 45 mg/m^2, Ida12: idarubicin 12 mg/m^2, Ida8: idarubicin 8 mg/m^2, Ida9: idarubicin 9 mg/m^2, 7 + 3: 7 days of cytarabine and 3 days of anthracycline, CR: complete remission, EFS: event-free survival, OS: overall survival.

Table 2.
Summary of trials comparing idarubicin and daunorubicin.

neutropenia, cardiotoxicity and overall survival between the 2 drugs. The second study also showed that idarubicin was associated with improved rates of complete remission as well as overall survival, compared to daunorubicin [16, 40].

A summary of the trials comparing idarubicin and high dose daunorubicin is presented in **Table 2.**

4. Mitoxantrone

Mitoxantrone, an anthraquinone derivative, has been extensively used with cytarabine as part of induction chemotherapy in patients with AML. It has been shown to be equally effective, if not better, when compared to daunorubicin. Nonetheless, it has not been adapted readily into the clinical practice of upfront induction chemotherapy and is often incorporated into the treatment algorithm in the relapse and refractory setting. There are 2 randomized trials comparing mitoxantrone, idarubicin and daunorubicin which will be discussed in the subsequent section.

The AML-10 study was a randomized phase III study comparing daunorubicin, idarubicin and mitoxantrone in 2157 patients, ≤60 years of age, with AML [41]. Remission induction was not given in the traditional 7 + 3 manner and consisted of cytarabine 100 mg/m^2 on days 1–10, etoposide 100 mg/m^2 on days 1–5 and either daunorubicin 50 mg/m^2, idarubicin 10 mg/m^2 or mitoxantrone 12 mg/m^2 on days 1, 3 and 5. A second round of the same regimen was given to those with a partial remission to the first round.

There was no difference in the rate of complete remission between the 3 anthracyclines. Nearly a quarter of patients, in each arm, proceeded to allogeneic stem cell transplant. After a median follow-up of 5.6 years, there was no difference in median and 5-year overall survival between the 3 arms. Even after adjusting for other variables, the results remained the same. For patients without a donor, the disease-free survival and survival from complete remission were longer in the idarubicin and mitoxantrone arm than in the daunorubicin arm. There was no difference for patients with a donor.

An ECOG phase III compared daunorubicin 45 mg/m^2, idarubicin 12 mg/m^2 and mitoxantrone 12 mg/m^2, given with continuous cytarabine, as 7 + 3 in older adults with AML [42]. The study enrolled 362 patients with a median age of 67 years. A second round of the same induction was given to patients with residual disease (>5% blasts) on day 14 bone marrow biopsy. There was no statistically significant difference for the rates of complete remission between the 3 arms. Furthermore, there was no difference observed in terms of toxicity profile, disease-free survival and overall survival between the 3 induction regimens.

5. CPX-351 (Vyxeos)

CPX-351 is a liposomal encapsulation of cytarabine and daunorubicin at a fixed synergistic molar ratio of 5:1. Using ratio-metric dosing, instead of the traditionally used maximum tolerated dose (MTD), potentially enhances the efficacy of drugs by maintaining the fixed drug ratio for a longer time in the blood. In the conventional form (MTD), the blood concentration or ratio of the drug(s), after infusion, may change immediately depending on the individual agent's pharmacokinetics, raising concern for inferior efficacy. A liposomal encapsulation, by evading first pass metabolism, may overcome this concern and lead to greater uptake by leukemia cells. Through this mechanism, an increased cytotoxic effect of the drugs

is observed, leading to prolonged myelosuppression, in addition to apoptosis of leukemia cells [43, 44].

The liposome of daunorubin:cytarabine 44 mg/m^2:100 mg/m^2 is FDA approved for the treatment of adults with therapy related AML or AML with myelodysplasia-related changes. A phase III study compared cytarabine + liposomal daunorubicin (CPX-351, Vyxeos) to 7 + 3 (daunorubicin 60 mg/m^2), in older patients (60–75 years) with secondary AML. The study enrolled 309 patients. CPX-351 was associated with a higher remission rate (47.7% vs. 33.3%, p = 0.016) as well as improved median overall survival (9.6 m vs. 5.9 m, HR 0.69, p = 0.003) compared to 7 + 3. There was no difference in early mortality between the two treatments. Prolonged neutropenia and thrombocytopenia were observed with CPX-351 [19].

Although the study above was limited to older patients, the FDA approved CPX-351 for all adults. The reason being that therapy related AML or AML with myelodysplasia-related changes are thought to be biologically aggressive subtypes, regardless of age. Whether CPX-351 is superior, in patients <60 years old, to 7 + 3 using either daunorubicin 90 mg/m^2 or idarubicin is not known. The results of ongoing studies in younger patients as well as planned clinical trials using CPX-351 in combination with targeted therapy or immunotherapy should help identify additional subsets of patients that may derive benefit from this drug.

6. Conclusion

AML is a heterogenous disease and the treatment plan for every patient is different. Both patient and disease related variables help determine the appropriate treatment option for each case. It is challenging to state the outright superiority of one anthracycline over another, but some useful conclusions can be drawn from the evidence presented above.

When choosing between 45 mg/m^2, 60 mg/m^2 and 90 mg/m^2 of daunorubicin, it is reasonable to look at patient age and cytogenetic and molecular abnormalities (if available in a timely manner), before picking one. Daunorubicin 45 mg/m^2 should be used for older patients >65 years of age based on the available evidence. It is probably safe and effective to use daunorubicin 60 mg/m^2 in this age group, but unfortunately there is lack of randomized data to support one dose over the other. For patients younger than 65 years of age, daunorubicin 90 mg/m^2 is superior to daunorubicin 45 mg/m^2. All cytogenetic risk categories and FLT3, NPM1 and DNMT3A-mutant AML seem to derive benefit from daunorubicin 90 mg/m^2. However, data is emerging to suggest that daunorubicin 60 mg/m^2 can effectively replace daunorubicin 90 mg/m^2.

Idarubicin is superior to daunorubicin 45 mg/m^2, when used as 7 + 3, in younger patients. It also appears to be as safe and effective as daunorubicin 90 mg/m^2, except for FLT3-mutant AML where daunorubicin 90 mg/m^2 may have a slight advantage. One caveat to the idarubicin vs. high dose daunorubicin studies is the small representation of older patients (>65 years). For older patients fit for intensive therapy, daunorubicin 45 mg/m^2, may still be the first choice.

Mitoxantrone is comparable to both idarubicin and daunorubicin. It's use in upfront therapy is still not as common as the other 2 available agents. CPX-351 should be the first choice in patients with secondary AML.

Whereas novel drug regimens are emerging in the treatment of AML, intensive chemotherapy still plays a significant role. Anthracyclines will serve as the backbone of AML treatment in fit patients and therefore it is important to know which type and dose to select in the appropriate setting.

Conflict of interest

The authors declare no conflict of interest.

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