
Idarubicin: An Anthracycline For Acute Myelogenous Leukemia

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Citation

L Alnaim. *Idarubicin: An Anthracycline For Acute Myelogenous Leukemia*. The Internet Journal of Oncology. 2007 Volume 5 Number 2.

Abstract

Objective: To review the scientific literature evaluating the efficacy and tolerability of Idarubicin, an anthracycline indicated for treatment acute myelogenous leukemia (AML) including French-American-British (FAB) classifications M1 through M7

Data sources: Articles were identified through searches of MEDLINE (1966–April 2007) using the key words idarubicin (IDA), acute myelogenous leukemia, anthracyclines. Additional citations were identified from bibliographies of publications cited.

Study selection and data extraction: Experimental and observational studies of IDA were selected. Trials of the efficacy of the drug in humans were the focus of the review.

Data synthesis: IDA is an effective alternative for the treatment of different types of AML. It significantly increases complete response rate and survival time when used in combination with other antileukemic drug. In comparative studies, there was a trend toward the superiority of IDA over daunorubicin. However, these data are insufficient to recommend IDA as a replacement for daunorubicin, and further studies will be required to ascertain if statistically significant differences in efficacy exist between the two drugs.

Conclusions: Current available clinical trials do not show advantage of one anthracycline over another. However, for APL the combination of all-trans retinoic acid and anthracycline induction therapy represents the mainstay of therapy.

INTRODUCTION

Acute myelogenous leukemia (AML) is a hematological malignancy characterized by replacement of the normal bone marrow by a malignant clone of immature blast cells derived from the myeloid series. Consequently, there is an excessive accumulation in the bone marrow and peripheral blood of immature blood cells which are functionally useless. AML is usually subdivided according to the French-American-British (FAB) classification, depending on the predominant differentiation pathway and the degree of maturation. Most of the clinical manifestations are related to bone marrow failure, causing infection and bleeding, and the effects of infiltration of organs by malignant cells. The most common presenting symptoms include weakness, lethargy, and pallor due to anemia.

At the outset, intensive combination chemotherapy is given in the hope of achieving a complete response (CR). The initial phase is termed induction. A CR can only be achieved

by virtual ablation of the bone marrow followed by recovery of normal hematopoiesis. The pyrimidine analogue cytarabine has been the basic treatment for the last 20 years. The addition of anthracyclines has increased CR rates. After the initial induction, additional post remission treatments are needed. Intensive consolidation with high dose cytarabine appears to dramatically improve survival rates^{1,2}. Idarubicin (IDA) is a DNA-intercalating analog of daunorubicin which has an inhibitory effect on nucleic acid synthesis and interacts with the enzyme topoisomerase II. It is used in the treatment of acute leukemia and solid tumors especially AML. We reviewed the use of IDA for the therapy of AML.

DATA SOURCES

We identified and reviewed clinical trials evaluating the efficacy of IDA through a MEDLINE search (1966–April 2007). Key words included idarubicin, acute myelogenous leukemia, anthracyclines. References from selected papers were also reviewed for additional citations, as well as online

resources pertaining to AML guidelines and management.

CLINICAL PHARMACOLOGY

IDA is an anthracycline analogue of daunorubicin. It is 5 to 6 times more potent and less cardiotoxic than daunorubicin. The mechanism of action of anthracyclines is poorly understood. Cytotoxicity is generally attributed to intercalation of the drug into DNA and/or inhibition of DNA topoisomerase II activity resulting in double and single strand DNA breaks. ^{1,3} IDA (4-demethoxydaunorubicin) is used in the treatment of acute leukemia and solid tumors. The only structural difference from the parent compound, daunorubicin, is lack of the methoxyl group at the C4 position of the aglycone. ^{2,4} IDA has a higher affinity for lipids than other anthracyclines, suggesting the possibility of good oral absorption. Subsequent studies demonstrated good biologic activity of the drug following oral administration. ^{3,5} Oral therapy would be an advantage over daunorubicin and doxorubicin, which are relatively inactive when administered orally. At oral doses of 3.5 times the intravenous dose, IDA exhibited activity equivalent to that of intravenous doxorubicin and daunorubicin in various murine leukemias. ^{4,5,6,7}

IDA has an affinity for DNA similar to the parent compound and somewhat higher efficacy than daunorubicin in stabilizing the DNA double helix against heat denaturation. IDA has been at least as active as daunorubicin in inhibiting 3H-TdR uptake by DNA or RNA of mouse embryo fibroblasts. ^{6,8}

PHARMACOKINETICS

Pharmacokinetic studies have been performed in adult leukemia patients with normal renal and hepatic function following intravenous administration of 10 to 12 mg/m² of IDA daily for 3 to 4 days, as a single agent or combined with cytarabine (Cytarabine). The plasma concentrations of IDA are best described by a two or three compartment open model. The disposition profile shows a rapid distributive phase with a very high volume of distribution presumably reflecting extensive tissue binding. The plasma clearance is twice the expected hepatic plasma flow indicating extensive extra hepatic metabolism. The drug is eliminated predominately by biliary and to a lesser extent by renal excretion, mostly in the form of the primary metabolite, 13-dihydroidarubicin (idarubicinol). ^{9,10,11}

The elimination rate of IDA from plasma is slow with an estimated mean terminal half-life ($t_{1/2}$) of 22 hours (range: 4

to 46 hours) when used as a single agent and 20 hours (range: 7 to 38 hours) when used in combination with cytarabine. The elimination of idarubicinol is considerably slower than that of the parent drug with an estimated $t_{1/2}$ that exceeds 45 hours; hence its plasma levels are sustained for a period greater than 8 days. As idarubicinol has cytotoxic activity it presumably contributes to the effects of IDA.

^{9,10,11,12,13}

The extent of drug and metabolite accumulation predicted in leukemia patients for Day 2 and 3 of dosing, based on the mean plasma levels and half-life obtained after the first dose, is 1.7- and 2.3-fold, respectively, and suggests no change in kinetics following a 3 day regimen. ^{13,14}

Studies of cellular (nucleated blood and bone marrow cells) drug concentrations in leukemia patients have shown that peak cellular IDA concentrations are reached a few minutes after injection. IDA and idarubicinol concentrations in the cells are more than a hundred times the plasma concentrations. IDA disappearance rates in plasma and cells were comparable with a $t_{1/2}$ of about 15 hours. The $t_{1/2}$ of idarubicinol in cells was about 72 hours.

Protein binding was studied in vitro by equilibrium dialysis at concentrations of IDA and idarubicinol similar to the maximum plasma level obtained in the pharmacokinetic studies. The percentages of IDA and idarubicinol bound to plasma proteins averaged 97% and 94%, respectively. The binding is concentration independent.

Cerebrospinal fluid (CSF) levels of IDA and its active metabolite, idarubicinol, were measured in pediatric leukemia patients treated intravenously. IDA was detected in 2 of 21 CSF samples (0.14 and 1.57 ng/mL), while idarubicinol was detected in 20 of 21 CSF samples obtained 18 to 30 hours after dosing (mean = 0.51 ng/mL, range 0.22 to 1.05 ng/mL). The clinical relevance of these findings is currently being evaluated. ^{4,9,10,11,12,13,14,15}

Figure 1

Table 1: General Pharmacokinetics *

Oral Absorption	rapid but erratic absorption, about 30% bioavailability
Distribution	bone marrow, extensive tissue uptake and plasma protein binding
Cross blood brain barrier?	Yes
Vd	64 L/kg
PPB	94-97%
Metabolism	Mainly in liver
active metabolite(s)	Idarubicinol
inactive metabolite(s)	Yes
Excretion	eliminated by biliary and renal excretion, mostly as idarubicinol
feces	17% (IV) 8% (oral) over 5 days
urine	16% (IV) 5% (oral) over 4 days
t½ α	5-30 minutes
t½ β	1-22 hours
t½ γ	15-35 hours
Cl	122.8 L/hour

* (Prod Info Idamycin® 2003)^{9, 15}

PEDIATRIC PATIENTS

IDA studies in pediatric leukemia patients, at doses of 4.2 to 13.3 mg/m² /day x 3, suggest dose independent kinetics. There is no difference between the half-lives of the drug following daily x 3 or weekly x 3 administration.^{9,16}

HEPATIC AND RENAL IMPAIRMENT

The pharmacokinetics of IDA has not been evaluated in leukemia patients with hepatic impairment. It is expected that in patients with moderate or severe hepatic dysfunction, the metabolism of IDA may be impaired and lead to higher systemic drug levels. The disposition of IDA may be also affected by renal impairment. Therefore, a dose reduction should be considered in patients with hepatic and/or renal impairment.^{4,9,10,11,12,13,14}

ADVERSE EFFECTS

MYELOSUPPRESSION

A major dose limiting side effect. Severe myelosuppression is the major toxicity associated with IDA therapy, but this effect of the drug is required in order to eradicate the leukemic clone. During the period of myelosuppression, patients are at risk of developing infection and bleeding which may be life-threatening or fatal.

GASTROINTESTINAL

Nausea and/or vomiting, mucositis, abdominal pain and diarrhea were reported frequently, but were severe (equivalent to WHO Grade 4) in less than 5% of patients. Severe enterocolitis with perforation has been reported rarely. The risk of perforation may be increased by instrumental intervention. The possibility of perforation should be considered in patients who develop severe abdominal pain and appropriate steps for diagnosis and management should be taken.

DERMATOLOGIC

Alopecia was reported frequently and dermatologic reactions including generalized rash, urticaria, and a bullous erythrodermatous rash of the palms and soles have occurred. The dermatologic reactions were usually attributed to concomitant antibiotic therapy. Local reactions including hives at the injection site have been reported.

HEPATIC AND RENAL

Changes in hepatic and renal function tests have been observed. These changes were usually transient and occurred in the setting of sepsis and while patients were receiving potentially hepatotoxic and nephrotoxic antibiotics and antifungal agents. Severe changes in renal function (equivalent to WHO Grade 4) occurred in no more than 1% of patients, while severe changes in hepatic function (equivalent to WHO Grade 4) occurred in less than 5% of patients.

HYPERURICEMIA

This can occur during periods of active cell lysis, which is caused by cytotoxic chemotherapy of highly proliferative tumors of massive burden (e.g., some leukemias and lymphomas), and can be minimized with allopurinol and hydration. In hospitalized patients the urine may be alkalinized, by addition of sodium bicarbonate to the intravenous fluids, if tumor lysis is expected.

CARDIAC

Acute life threatening arrhythmias have been occasionally described during therapy. Cardiac toxicity is as described for other anthracyclines, although it may be less than with doxorubicin or daunorubicin. Cardiac toxicity is manifested by congestive heart failure or by a decrease in left ventricular ejection fraction, may occur during or several weeks after therapy. There is no currently recommended maximum cumulative lifetime dose for IDA, but the incidence is low with cumulative doses of < 400mg/m² when given orally. The risk of cardiotoxicity is increased with cardiac radiation, advanced age, in the setting of sepsis, anemia, other cardiac abnormalities or prior exposure to anthracyclines or other cardiotoxic agents.

Careful monitoring is advisable, particularly if there is significant exposure to other cardiotoxic drugs, a history of cardiac disease or a history of thoracic radiation. In patients with AML and myelodysplasia (MDS) who received IDA-based induction and post remission or salvage therapy, IDA-related cardiomyopathy was uncommon with cumulative

IDA doses of up to 290 mg/m². Asymptomatic LVEF decreases were more frequent.¹⁷

EXTRAVASATION

The tissue necrosis that occurs may happen days to weeks after the treatment. Patients must be observed for delayed reactions and prior injection sites carefully inspected. A central line access is advisable for injection of anthracyclins. Local erythematous streaking along the vein and facial flushing may result from too rapid administration.

RADIATION RECALL REACTIONS

IDA has the potential to enhance radiation injury to tissues. The timing of the radiation may be before, concurrent with, or even after the administration of the IDA. Recurrent injury to a previously irradiated site may occur weeks to months following radiation.^{5,9,11,18}

Figure 2

Table 2: Major Adverse Effect by organ Site*

Organ Site	Side effect	Onset
Cardiovascular	Arrhythmias, bundle branch block (rare, transient)	I
	Thromboembolism	I
	Pericarditis/myocarditis (rare)	I
Dermatologic	<u>Congestive heart failure (serious 2%)</u>	D L
	Alopecia (75%, usually partial)	E
	Rash, urticaria, nail changes	E
	Facial flushing with rapid injection	I
Extravasation hazard	VESICANT	I
	Nausea and vomiting (80%)	I
Gastrointestinal	Anorexia	E
	Typhilitis, GI bleeding, perforation (rare)	E
	Stomatitis (appears day 3-10) (50%)	E
Hematologic	<u>Myelosuppression</u>	E
	Nadir 7-14 days, recovery 21-24 days	
Hepatic	Transient elevation of liver function tests (20-30%)	E
	Rash, fever, chills	I
Hypersensitivity	Anaphylaxis (rare)	I
	Flare reaction (histamine release)	I
Injection site	Chemical phlebitis	I
	Secondary leukemia	L
Neoplastic	Infertility, menopausal symptom	E
	Hyperuricemia	I
Renal/metabolic	Red coloration of urine for 1-2 days	I

Dose-limiting side effects are underlined, I = immediate (onset in hours to days), E = early (days to weeks); D = delayed (weeks to months); L = late (months to years)

*Krogh (1993)¹², Fields (1991)⁴⁷, Cersosimo (1992)⁴⁸

CLINICAL TRIALS

ACUTE MYELOID LEUKEMIA (AML)

IDA is effective in combination regimens for treatment of acute no lymphocytic leukemia (ANLL). Single agent IDA in doses of 8 to 12 mg/m² daily for 3 days has been effective in refractory or relapsed adult and pediatric ANLL.

Response rates have ranged from 25% to 50%.^{16,18,19,20}

There is evidence of non-cross resistance with IDA and other agents used in the treatment of acute leukemia, including other anthracyclines, cytarabine, amsacrine, and etoposide.²¹ Long-term survival is achieved in

approximately 20% to 30%.²² IDA is usually used in a two-drug combination with both standard and high-dose cytarabine, as well as in 3-drug combinations with etoposide plus standard or high-dose cytarabine. CR rates of up to 70% within one or two cycles can be expected in previously untreated patients.^{21,23,24}

In an open Phase II trial (n=43), untreated patients younger than 60 years of age with AML were induced with a regimen of IDA (8 mg/m² on days 1 through 5 or 12 mg/m² on days 1, 3, and 5), etoposide (100 mg/m² on days 1 through 5) and carboplatin 1000-1500 mg/m² as a continuous infusion on days 1 through 5) elicited a 67% CR rate. Those who achieved remission received a high-dose cytarabine consolidation regimen 4 weeks later and experienced a median 15.4 months leukemia-free survival. Median overall survival was 12.5 months. The prognosis was especially poor for those with very complex karyotypes. Grade 3 to 4 diarrhea, nausea, and stomatitis occurred in 33%, 26% and 23%, respectively, with bacteremia/fungemia reported in 49%. The authors concluded that this regimen offered no advantages over standard protocols and did not warrant Phase III study.²⁵

Among 52 patients with either newly diagnosed or therapy induced AML, a 72% remission rate was observed within one treatment cycle using IDA, high-dose cytarabine, plus etoposide. This is higher than historically achieved with a 2-drug combinations (58%), but the difference was not statistically significant. When followed by unpurged bone marrow transplant, survival in the patients receiving triple therapy was greater than historical controls. Relapse rate was 26% following triple therapy, compared to 72% with double therapy. Disease-free survival rates were 65% versus 18%, respectively. At 5 years from diagnosis, 50% of patients who received triple therapy were alive.¹⁹ The combination of IDA, etoposide, and cytarabine in untreated patients (mean age, 40 years) with ANLL resulted in a CR in 25 of 31 patients (81%), with higher responses occurring in younger patients.²⁶

Oral single-agent IDA (20 to 25 mg/m² /day for 3 days) has demonstrated efficacy in ANLL and as palliative treatment in patients with chronic myelogenous leukemia in accelerated phase or blast crisis.^{19,27,28,29} A randomized multicenter study was conducted among 92 patients over 65 years of age with newly diagnosed AML to compare oral treatment with etoposide, thioguanine and IDA (ETI) to an intravenous combination of cytarabine, IDA, and

thioguanine (TAI). Patients first received a six day intravenous treatment with cytarabine and IDA. After the first treatment, 68 patients were randomized to receive two cycles of ETI (n = 36) or TAI (n = 32) and thereafter maintenance with mercaptopurine and methotrexate. Of the 92 patients, 52 (57%) achieved remission at some stage. The median survival was 10 months. There were no significant differences between the two groups regarding remission rates (67% vs. 72%), survival (12 mo), event-free survival, or relapse rates. The patients who received ETI spent significantly fewer days in the hospital (20 vs. 41 days, $P = 0.010$), and they had fewer days with infusions, shorter neutropenias and thrombocytopenias and fewer and less severe infections. Treatment with oral ETI resulted in a similar antileukemic effect as obtained with intravenous administration of TAI, with less toxicity and reduced need for hospitalisation. ³⁰

ACUTE PROMYELOCYTIC LEUKEMIA (APL)

The combination of all-trans retinoic acid (ATRA) with an anthracycline is an effective remission-induction therapy for newly-diagnosed APL. Maintenance therapy using alternating cycles of methotrexate plus 6-mercaptopurine followed by ATRA alone is effective in maintaining CR, as well as prolonging the survival of patients with APL.

At present ATRA represents the mainstay of APL treatment. Current available clinical trials show that the combination of ATRA and anthracycline induction therapy produces approximately 90% CR rate and seems to significantly improve disease-free survival. ³¹

The Gruppo Italiano per le Malattie Ematologiche dell'Adulto (GIMEMA) group initiated a randomized study comparing IDA alone at 10 mg/m² daily for 6 consecutive days (arm A) with IDA at 12 mg/m² daily for 4 days and cytarabine at 200 mg/m² as a daily continuous infusion for 7 days (arm B) as induction treatment in patients with newly diagnosed hypergranular acute promyelocytic leukemia (APL). Of the 257 patients evaluable for induction treatment, 131 were randomized to arm A and 126 to arm B. Once in CR, patients received 3 consolidation courses of standard chemotherapy, and those still in CR at the end of consolidation were randomized to receive or not receive 1 mg/kg of 6-mercaptopurine daily and intramuscular injections of 0.25 mg/kg methotrexate weekly for 2 years. Overall, 100 (76.3%) patients in arm A and 84 (66.6%) patients in arm B achieved CR. This difference is not statistically significant. Event-free survival rates were 35%

and 23% in arm A and B, respectively ($P = .0352$). These results indicate that monochemotherapy with IDA may not be inferior to a cytarabine-based regimen in patients with newly diagnosed APL. ³²

The initial clinical manifestation of pediatric APL does not differ much from that of AML. However, severe bleeding is the hallmark of APL. APL has traditionally been managed similarly in children and adults. The majority of treatment protocols include both pediatric and adult patients. Although outcomes in children and adults with APL have been comparable, there is increasing concern that the anthracycline dose intensity may cause long-term cardiac dysfunction in a substantial proportion of patients. In a multicenter study by the PETHEMA Group in children with genetically proven APL who received induction therapy with ATRA and IDA. Sixty-one out of 66 (92%) achieved CR. Early deaths from hemorrhage and retinoic acid syndrome occurred in three patients and two patients, respectively. No deaths in CR, clinical cardiomyotoxicity, or secondary malignancy occurred. The 5-year cumulative incidence of relapse was 17%, whereas disease-free survival and overall survival rates were 82% and 87%, respectively. This regimen showed an antileukemic efficacy comparable to those previously reported regimens with other chemotherapy combinations in children. ³³

In the GIMEMA group experience, 107 children with APL were eligible and evaluable for induction, and were treated with ATRA and IDA induction followed by 3 polychemotherapy consolidation courses. 103 (96%) achieved CR. The overall survival and event-free survival were 89% and 72% respectively. ³⁴

Chemotherapy in elderly patients with APL has been reported as less effective than in younger patients. Patients older than 60 years with APL who were enrolled in two successive multicenter studies received induction therapy with ATRA and IDA, consolidation with 3 anthracycline courses with or without ATRA, and maintenance with ATRA and low-dose chemotherapy. Eighty-four percent of 104 patients achieved CR. One patient showed molecular persistence after consolidation and 5 had a relapse. The 6-year cumulative incidence of relapse, leukemia-free survival, and disease-free survival were 8.5%, 91%, and 79%, respectively. A significantly higher incidence of low-risk patients found among the elderly, as compared to younger patients, may partially account for the low relapse rate observed. This study confirms the high antileukemic

efficacy, low toxicity, and high degree of compliance of protocols using ATRA and IDA for induction and consolidation therapy in elderly patients.³⁵ In another non-randomized study, 134 elderly patients with newly diagnosed APL were enrolled in two successive protocols of the Italian multicenter group GIMEMA. All patients received an identical induction with ATRA and IDA; Of the 134 patients, 116 (86%) had CR, 2% were resistant, and 12% died during induction. After CR, 106 patients received further therapy whereas 10 did not, because of refusal (n=5) or toxicity (n=5). Of these 106 patients, 67 received the AIDA consolidation therapy and 39 an amended AIDA (aAIDA) therapy. The AIDA protocol consisted of a first course with IDA 5 mg/m² and cytarabine 1 g/m² on days 1 to 4; a second course with mitoxantrone 10 mg/m² and etoposide 100 mg/m² on days 1 to 5; and a third course with IDA 12 mg/m² on day 1, cytarabine 150 mg/m² subcutaneously every 8 hours on days 1 to 5, and 6-thioguanine 70 mg/m² every 8 hours on days 1 to 5. The aAIDA consisted of the first consolidation course of AIDA only.

In the AIDA group, 43 patients (64%) completed consolidation, while 27 (36%) withdrew after the first or second courses; 9 (13%) died in CR and 12 (18%) relapsed. In the aAIDA group, 2 (5%) died in CR and 6(15%) relapsed. In both groups, the 3-year overall and disease-free survival rates were 81 and 83%, and 73 and 72%, respectively.

This study confirms that incorporation of ATRA in front-line therapy has markedly improved APL prognosis also in elderly patients, allowing CR and survival rates that are similar to those achieved in younger patients and considerably higher than those of elderly patients with other AML subtypes. Using a reduced intensity post remission treatment might be appropriate in such patients. With the limits of a nonrandomized group comparison, outcome results point to a similar antileukemic effect of a single consolidation cycle that, as expected, carried significantly inferior toxicity as compared to the three consolidation courses administered in the original AIDA protocol.³⁶

COMPARATIVE EFFICACY

The combination of IDA/cytarabine has been at least as effective as daunorubicin plus cytarabine in untreated patients with ANLL. CR after 1 course was (60% to 80%) for patients treated with IDA/ cytarabine and (40% to 60%) with daunorubicin/ cytarabine. Bone marrow suppression

was more prolonged with idarubicin/cytarabine as was gastrointestinal toxicity (diarrhea), while cardiotoxicity may be worse with daunorubicin.^{37,38,39,40} Collectively, studies have suggested a trend toward the superiority of idarubicin over daunorubicin. With regard to adverse effects, two of these studies reported similar toxicity profiles, whereas others reported a lower frequency of serious vomiting with IDA, although diarrhea was more prevalent with IDA. Moreover, oral or esophageal mucositis was more common and myelosuppression more prolonged with the IDA regimen. Cardiotoxicity (QRS voltage reduction, prolongation of the QTs) was similar in some studies with IDA and daunorubicin while significantly worse during daunorubicin in others.^{38,40}

Figure 3

Table 3: Comparative Clinical Trials In Adult AML

	Patient Characteristics		Doses as mg/m ²		CR rate		Overall survival (months)	
	Randomized patients	Median age	IDR	DNR	IDR	DNR	IDR	DNR
Berman (1991) ³⁷	130	36.5 (17-61)	12	50	80%	58%*	19.5	13.5*
Vogler (1992) ³⁸	214	56 (17-85)	12	45	71%	58%*	9.7	9.1
Wiernik (1992) ³⁹	208	60.5 (17-82)	13	45	70%	59%	12.9	8.7*
Mandelli (1991) ³⁸	249	62 (55-78)	12	45	40%	39%	3	6
Masaoka (1996) ³²	64		12	40	59.4%	40.6%*	NA	NA
Reiffers (1996) ⁴⁰	220		8	50	68%	61%	NA	NA

* statistically significant, IDA: Idarubicin, DNR: Daunorubicin, CR: Complete response NA, not available.

In comparative trials, in 91 newly diagnosed ANLL patients, CR was achieved in 36 of 45 patients (80%) treated with IDA/cytarabine and in 24 of 41 (58%) receiving daunorubicin/cytarabine. Significantly more patients in the IDA group achieved remission following 1 course of therapy (75% versus 46%) and the time to CR was also shorter in IDA/cytarabine treated patients (33 versus 43 days). Treatment regimens included standard combination of cytarabine plus daunorubicin (50 mg/m² /day for 3 days) or cytarabine plus IDA (12 mg/m² /day for 3 days). In both regimens, cytarabine was administered at a dose of 200 mg/m² /day for 5 days. A second course of therapy was given to patients not achieving an aplastic marrow by day 14. Patients achieving CR received 2 courses of consolidation therapy. Survival curves demonstrated a significant advantage in the IDA/cytarabine group. Non-hematologic toxicity was similar in each group, with the main toxic effects being nausea, vomiting, and mucositis; no cases of congestive heart failure were observed in either group.^{37,38,40}

IDA was compared with daunorubicin, when used with cytarabine as induction chemotherapy for newly diagnosed AML. There were 1052 patients in five trials of IDA versus daunorubicin. CR rates were higher with idarubicin (62% vs 53%; $P=0.002$). Among remitters, fewer of the patients allocated to IDA relapsed ($P=0.008$) but slightly more died in remission, leading to a non-significant benefit ($P=0.07$) in DFS. Overall survival in these five trials was significantly better with idarubicin than with daunorubicin (13% vs 9% alive at 5 years; $P=0.03$). There was a trend ($P=0.006$ for remission rate) for the benefit of idarubicin over daunorubicin to decrease with increasing age. The induction regimens based on idarubicin achieved better remission rates and better overall survival than those based on daunorubicin.⁴¹ The only subgroup effect that was of statistical significance was that the advantage of IDA seemed less definite in older patients.^{42,43,44,45,46}

A collaborative overview, using individual patient data, has been performed to compare idarubicin versus daunorubicin or other anthracyclines, when used with cytarabine as induction chemotherapy for newly diagnosed AML. There were 1052 patients in five trials versus daunorubicin, 100 in one trial versus doxorubicin, and 745 in one trial versus zorubicin. In the trials of idarubicin versus daunorubicin, early induction failures were similar with the two treatments (20% IDA vs 18% daunorubicin; $P=0.4$), but after day 40 the later induction failures were fewer with IDA (17% vs 29%; $P < 0.0001$). Therefore CR rates were higher with IDA (62% vs 53%; $P=0.002$). Among remitters, fewer of the patients allocated to IDA relapsed ($P=0.008$) but slightly more died in remission, leading to a non-significant benefit ($P=0.07$) in disease-free survival. Overall survival in these five trials was significantly better with IDA than with daunorubicin (13% vs 9% alive at 5 years; $P=0.03$). There was a trend ($P=0.006$ for remission rate) for the benefit of IDA over daunorubicin to decrease with increasing age. There were no significant differences in outcome in the small trial comparing IDA versus doxorubicin, or in the large trial comparing IDA versus zorubicin.⁴¹

CONTRAINDICATIONS AND PRECAUTIONS

IDA is contraindicated in cases of known hypersensitivity to IDA or other anthracyclines. Patients, who have marked myelosuppression induced by previous treatments with other antitumor agents or by radiotherapy should have their IDA modified or delayed. Cardiac toxicity is cumulative across members of the anthracycline (doxorubicin, epirubicin, daunorubicin, IDA) and anthracenedione (mitoxantrone)

class of drugs. Patients who have received these agents are at increased risk of toxicity, and should be carefully monitored. Moreover, IDA is contraindicated in severe renal and liver impairment and uncontrolled infections. IDA has been shown to have mutagenic and carcinogenic properties in rats. Its safe use in pregnancy and its effects on fertility have not been established. Breast feeding is not recommended due to the potential secretion into breast milk.^{12,47}

INDICATIONS

FDA Approved Indications include treatment of AML in adults in combination with other approved antileukemic drugs. This includes French-American-British (FAB) classifications M1 through M7.⁹ Other indications which are not approved by FDA, but have shown to be effective include, acute lymphocytic leukemia, breast cancer, chronic myelogenous leukemia, and non-Hodgkin's lymphoma.^{3,12,16,18,22,24}

DOSAGE AND ADMINISTRATION

Numerous dosing schedules exist depending on the disease, expected response, and concomitant therapy. Guidelines for dosing also include consideration of white blood cell count. Dosage may be reduced and/or delayed in patients with bone marrow depression due to cytotoxic/radiation therapy.^{9,16,48} For treatment of AML in adults, IDA is used for induction, at a dose of 12 mg/m^2 intravenously daily for 3 days in combination with cytarabine. For consolidation, a dose $10\text{-}12 \text{ mg/m}^2$ intravenously daily for 2 days every three weeks is used. In patients with unequivocal evidence of leukemia after the first induction course, a second course may be administered. Administration of the second course should be delayed in patients who experience severe mucositis, until recovery from toxicity has occurred, and a dose reduction of 25% is recommended.^{47,49}

Figure 4

Table 4: Parenteral Administration*

Subcutaneous, Intramuscular	not used due to corrosive nature
Direct intravenous	<ul style="list-style-type: none"> Preferred method due to need for frequent monitoring for signs of extravasations. Push slowly, so that drip of IV solution does not stop or reverse. Doses may be mixed in 50mL mini bag (5% Dextrose); Infuse through sidearm of free flowing IV over 10-20 minutes. Slow down injection rate if erythematous streaking occurs. When admixed with heparin, precipitation may occur.
Intermittent infusion	not recommended in children: dilute in 15-20 mL and infuse over 15-30 minutes
Continuous infusion	not recommended
Intraperitoneal, Intrapleural, Intrathecal, Intra-arterial	no information available on these route
Intravesical	has been used as 1 hour instillation
Oral	<ul style="list-style-type: none"> Available as 5, 10 and 25 mg capsules Swallow whole with water; should not be chewed. May be taken with or without food.

*Mross (1992)³⁰, Cersosimo(1992)⁴⁹, Prod Info Idamycin® 2003⁹, Feig (1992)⁵¹

In case of myelosuppression, IDA dose should be modified. In addition doses should be adjusted in case of renal or hepatic dysfunction as described in the following equations:

Figure 5

Dosage in renal failure	Creatinine (µmol/L)	% of usual dose to be given
	>200	50

Dosage in hepatic failure	Bilirubin (µmol/L)	% of usual dose to be given
	>40<85	50
	>85	Omit

Dosing in the pediatric population has been defined for the treatment of acute lymphoid leukemia at a dose of 8-10 mg/m² /day intravenously for three days. ^{9,16,50}

CONCLUSIONS AND RECOMMENDATIONS

In acute leukemia patients, the results of 5 studies have indicated that IDA compares favorably with daunorubicin when administered in combination with cytarabine. Collectively, these studies suggested a trend toward the superiority of IDA over daunorubicin. Patient treated with induction regimens based on IDA appear to have a lesser probability of primary resistance to chemotherapy and a lower relapse risk. These regimens are usualluy substantially less toxic in terms of early induction failures and deaths in CR, leading to superior CR rates and better overall survival with IDA.

However, these data are insufficient to recommend IDA as a replacement for daunorubicin, and further studies will be required to ascertain if statistically significant differences in efficacy exist between the two regimens. With regard to adverse effects, IDA has not offered any meaningful advantage over daunorubicin in leukemia patients; although the frequency of serious vomiting was lower with

IDA/cytarabine in one study, mucositis was more common and myelosuppression more prolonged with the IDA regimen. Cardiotoxicity has been similar with IDA and daunorubicin. At present, IDA should be considered as an alternative to daunorubicin in the treatment of acute leukemia, particularly in relapsing patients as there may be some degree of lack of cross-resistance with IDA.

In the special case of APL, the combination of ATRA and anthracycline induction therapy represents the mainstay of APL treatment. Current available clinical trials do not show preference of one anthracycline over another, although most experience has been with IDA.

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