

REMISSION INDUCTION THERAPY FOR ADULTS WITH ACUTE MYELOGENOUS LEUKEMIA: TOWARDS THE *ICE* AGE?

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ABSTRACT

The primary goal of acute myeloid leukemia chemotherapy is to obtain a complete remission. In adults with *de novo* disease, response rates reach between sixty and seventy per cent with classical '3+7' or DAT schemes. Curative postinduction treatments are now available for responsive patients, which makes it mandatory to look for more effective modalities of induction therapy. Experience gathered in recent years shows that idarubicin, cytosine arabinoside, and etoposide together might contribute to the modeling of an improved remission induction regimen: ICE. Because ICE and similar programs are being used with increasing frequency worldwide, we decided to review critically the underlying issues and the evidence supporting this change.

Key words: AML, remission, ICE protocol

The background: '3+7' and DAT

Patients with acute myelogenous leukemia (AML) who benefit most from recent therapeutic advances are those aged up to 60 years with *de novo* disease, that is without an antecedent hematological disorder or one secondary to chemo-radiotherapy for another malignancy.¹

Although AML is more typically observed in the elderly and develops frequently in people with myelodysplastic states, it is only in this selected patient population that the intrinsic nature of the disease and patient tolerance to chemotherapy allow a relatively safe escalation of dose intensity, leading to appreciable remission rates. Responders are subsequently treated with intentionally curative regimens, including high-dose consolidation and bone marrow or peripheral blood stem cell transplants. Although long-term survivorship may vary considerably depending on risk factors and type of consolidation or transplant, and while debate continues over the most effective postinduction strategy, the concept that AML may be cured in adults has emerged.^{2,3}

In contrast, progress in the field of remission

induction therapy has been less satisfactory. Until very recently remission induction chemotherapy for AML in adults consisted of an anthracycline drug, most often daunorubicin (DNR) at 45 to 60 mg/m²/d, given for three days, along with seven days of conventional-dose cytarabine (ara-C) ('3+7' regimen). The addition of 6-thioguanine is presently regarded as unnecessary but was used by many in the past (DAT regimen). The use of adriamycin (ADR) or rubidazole instead of DNR has resulted in similar or minimally different results. One or two '3+7' or DAT courses are usually needed to achieve a complete remission (CR) in approximately 60-70% of cases (Table 1).⁴⁻¹⁶

What is the fate of the patients who do not enter a CR? First, many die of complications, mainly infectious, during the pancytopenic phase without clear evidence of leukemia regrowth. Others do not enter CR because of a primarily refractory disease, to which they succumb. The estimated incidence of resistant AML after '3+7'/DAT is between 15% and 20% (Table 1), and few of these patients are salvaged by alternative treatments.

Table 1. Complete remission rates from representative adult AML series treated with classical '3+7' or DAT-like regimens.

Study (ref.)	Regimen	No. of pts	CR %	Refractory %	Notes
German (4)	TAD-9	576 ¹	65	14	¹ including pts >60
CALGB 7921 (5)	'3+7'	211 ¹	53 ²	24	¹ including pts >60;
	'3+10'	241 ¹	57 ²	15	² CR rate is 65% in pts <60
	TAD	216 ¹	57 ²	17	
Roswell Park (6)	'3+7'	256 ¹	58	–	¹ including pts >60
EORTC AML6 (7)	'3+7'+VCR	515 ¹	67	18	¹ age 10-65
HOVON (8)	'3+7'/DAT	117	77	–	–
CALGB 8525 (9)	'3+7'	724	72	–	–
AMLCG 1985 (10)	TAD-9	755 ¹	69	–	¹ including pts >60
EORTC/GIMEMA					
AML8A (11)	'3+7'	737	67	23	age 45-60
AML8B (12)	'3+7'	423	61	22	age 10-45
SBH/BG/VI (13)	DAT ¹	396 ²	61	18	¹ with ADR 25 mg/m ² /dose; ² including secondary and MDS/AML
ECOG (14)	DAT ¹	744	71	18	¹ DNR 60 mg/m ² /dose
SWOG (15)	Rubidazone-OAP	147 ¹	54	–	¹ including pts >60
	Ad-OAP	464 ¹	54	–	
GIMEMA (16)	'3+7'	448	68	15	–

It follows that, in order to improve the CR rate, efforts should be directed at reducing both the number of pancytopenic deaths and the incidence of primarily refractory disease. The common thought in AML chemotherapy that *more is better* was the conceptual basis upon which trials subsequent to '3+7' and DAT were developed. Actually, it should not be forgotten that increasing the intensity of front-line treatment to overcome primary resistance could even be detrimental if associated with greater drug toxicity and toxic death rates. This possibility can only be dealt with by improving supportive treatment at the same time.

Nevertheless, the fact remains that improving the remission induction regimen is essential if more CR patients are to be offered potentially curative postremission therapy.

Newcomers: high-dose ara-C, mitoxantrone, AMSA, etoposide, idarubicin

During the last few years, the use of high-dose ara-C and other drugs as alternatives or in addition to anthracyclines has been extensively investigated. Several protocols were eventually

developed based on a wide range of ara-C schedules in combination with all of the new drugs, but there is presently a substantial lack of evidence suggesting a real therapeutic advantage for most of these programs. For the sake of brevity, we will refer primarily to the results of selected trials directly comparing the old and the new, and to innovative open studies conducted at renowned Institutions.

Although encouraging results were reported with mitoxantrone-etoposide in advanced AML,¹⁷ virtually no recent treatment for newly diagnosed AML excludes ara-C. Rather, ara-C has been used at intermediate to high doses¹⁸ ranging from 0.5 to 3 g/m² per dose, given twice daily for up to six days, almost always with anthracyclines¹⁹⁻²⁵ and recently with fludarabine.²⁶ Overall results varied from good to very good in the early reports (Table 2) but toxicity was substantial, especially in older age groups, who required a high level of supportive care, and, more importantly, results from randomized trials did not fulfill the initial hope that high-dose ara-C could represent a significant improvement.^{24,25}

Mitoxantrone and the acridine derivative

Table 2. Summary of representative adult AML trials evaluating high- or intermediate-dose (H/ID) ara-C.

Study (ref.)	Regimen	No. of pts	CR %	Refractory %	Notes
Johns Hopkins (19)	DNR/HDara-C	64 ¹	55	–	¹ including MDS/AML and >60
Vancouver (20)	DNR/HDara-C	70 ¹	90	2	¹ including MDS/AML
Toronto (21)	HDara-C/PDN	94	63	24	—
UCLA (22)	'3+7' DNR/IDara-C ²	51 ¹ 50 ¹	71 74	18 12	¹ including MDS/AML; ² intermediate dose ara-C
MD Anderson (23)	DNR/HDara-C ¹ HDara-C HDaraC+A/M ³	56 ² 110 ² 66 ²	48 65 74	32 14 14	¹ with GM-CSF; ² including >60 and MDS/AML; ³ A/M denotes AMSA or mitoxantrone
ALSG (24)	DNR/HDara-C DNR/ara-C	279 ¹	70 74	– –	¹ total no. of pts randomized
SWOG (25)	DNR/HDara-C DNR/ara-C	168 471	55-45 ¹ 59-64 ¹	– –	¹ age <50->50
MD Anderson (26)	FLAG ¹ FA	112 ² 85 ²	63 53	– –	¹ with G-CSF; ² including >60 and MDS/AML

FA denotes fludarabine plus HD ara-C; FLAG is FA plus G-CSF.

AMSA were compared directly to DNR and they gave similar or slightly better CR rates, but in these trials the results from the DNR control arm were perhaps lower than expected or than reported in other trials (Tables 1 and 3), casting doubts on the preferential use of either of these two drugs, which were nonetheless confirmed to exert a strong antileukemic activity.²⁷⁻³⁰

Etoposide is another drug useful in AML treatment, especially in association with ara-C, although uncertainty persists regarding the best way of using the two drugs together.^{31,32} Results obtained with etoposide-containing combina-

tions in refractory AML stimulated evaluation of this agent as part of front-line regimens.³³ First, an Italian collaborative trial showed that etoposide plus ara-C plus vindesine were as effective as a classical DAT scheme.³⁴ In a second step, a randomized study from Australia showed no increase of CR rate in patients receiving '3+7' plus etoposide, compared to those not given the drug but, interestingly, remission duration was considerably improved in the study arm in which etoposide was administered during both the induction and consolidation phases.³⁵ This discrepancy is diffi-

Table 3. Summary of representative adult AML trials evaluating AMSA, mitoxantrone, etoposide.

Study (ref.)	Regimen	No. of pts	CR %	Refractory %	Notes
MD Anderson (27)	AMSA-OAP Ad-OAP	134 ¹ 134 ¹	52 48	– –	¹ including pts >60 and MDS/AML
MSKCC (28)	DAT m-AMSA/AT	46 ¹ 46 ¹	54 70 ²	39 22	¹ including pts >60; ² better CR rate only in pts <50 (p .03)
Valhalla, NY (29)	'3+7' Mitoxantrone/ ara-C	50 48	69 80	20 1	difference not significant (p .1)
Vancouver (30)	Mitoxantrone/ HD ara-C/etoposide	62 ¹	77	11	¹ including MDS/AML
Bologna Univ. (34)	DAT VDS+ara-C/ etoposide	79 77	58 61	– –	– –
ALSG (35)	'3+7' '3+7'/etoposide	132 ¹ 132 ¹	59 56	5 ² 4 ²	¹ 19% of pts >60; ² after course III; CR duration was better in etoposide arm (p .01)

Ad is adriamycin, AT is araC plus thioguanine, VDS is vindesine.

Table 4. Complete remission rates from IDA-containing combinations in adult AML.

Study (ref.)	Regimen	No. of pts	CR %	Refractory %	Notes
MD Anderson (45)	IDA/HDara-C	77 ¹	83	–	¹ includes >60 and MDS/AML; compared to historical group: increased and faster CR
Roswell Park (46)	IDA/HDara-C	20 ¹ <i>de novo</i> 10 ¹ secondary	65 20	15 40	¹ includes >60; 90% CR rate in <i>de novo</i> AML <60; additional G-CSF used
UK AML (47)	IDA + various	69 ¹	57	–	¹ includes >60; 82% CR rate after course I; WBC level not affecting CR rate
Heidelberg Univ. (48)	IDA/ara-C	56	78	13	additional GM-CSF used
Milan Univ. (49)	IDA/ara-C	57	84	5	WBC count not affecting CR rate
Buenos Aires (50)	IDA/AT	47	66	23	–
Mexico (51)	IDA/HDara-C	26	70	19	–
GOELAM (52)	IDA/ara-C	121 ¹	67	18	¹ pt age 55-75; additional use of GM-CSF
Essen Univ. (53)	IDA/ara-C	47	68	23	–
Finnish Group (54)	IDA/ara-C	35 ¹	57	34	¹ pt age 22-74; all high-risk MDS or MDS/AML
EORTC (55)	IDA/ara-C	36 ¹	55	–	¹ all pts high-risk MDS or MDS/AML
MD Anderson (56)	IDA/HDara-C IDA/FLAG	98 ¹ 18 ¹	80 63	– –	¹ including pts >60 and MDS/AML; ± G-CSF

FLAG is fludarabine plus ara-C and G-CSF

cult to understand, yet it portends relevant issues. It is hard to admit that the cytotoxic power of etoposide may vary according to the leukemic cell burden, from low at presentation to greater at the time of morphological marrow remission. Alternatively, the nature if not the number of these remissions might be better. This view assumes that etoposide may contribute significantly to eradicating leukemia in etoposide-sensitive cases, most likely those who do not exhibit multi-drug resistant or decreased topoisomerase II phenotypes.³⁶ In such cases, a synergy with ara-C and anthracyclines can be assumed. In other words, remissions in etoposide-treated patients may well be better from the beginning, thus conferring a late prognostic benefit, while due to putative mechanisms of initial drug resistance their number would not change appreciably. Moreover, since in the ALSG study disease-free survival was improved by including etoposide from the first induction course, it appears much more practical to follow this same path when considering this drug for inclusion in front-line AML therapy.

Although idarubicin (IDA), chemically 4-

demethoxydaunorubicin, was synthesized almost 20 years ago, its entry into the restricted cohort of effective anti-AML drugs is relatively recent. *In vitro*, IDA is a powerful inhibitor of AML cell growth, more so than other anthracyclines.^{37,38} Long-lasting inhibitory concentrations of IDA and its active alcohol metabolite, idarubicinol (IDA-ol), are reached after a single intravenous injection with 10 mg/m². The estimated half-life of IDA and IDA-ol is nearly 35 and 100 hours, respectively, which greatly prolongs their cytotoxic effect. IDA but not DNR affects the growth of resting blood progenitor cells, including leukemic ones, and has the property of overcoming some multi-drug resistance phenotypes, at least *in vitro*.³⁸⁻⁴⁰ The activity of IDA alone or in combination with ara-C was first demonstrated in patients with refractory disease,⁴¹⁻⁴³ later to be confirmed in previously untreated patients.⁴⁴⁻⁵⁵ In these heterogeneous reports (Table 4), outcome and time to positive outcome were generally better and faster, respectively, than in historical DNR-treated controls, at least when such a comparison was made and in younger patients with no antece-

Table 5. Complete remission rates from randomized IDA studies in adult AML.

Study (ref.)	Regimen	No. of pts	CR %	Refractory %	Notes
MSKCC (57)	IDA/ara-C DNR/ara-C	60 60	80 58	13 35	IDA arm: higher CR rate (p .01), more CR after course I (p .005); WBC count not affecting CR rate (p .04)
GIMEMA (58)	IDA/ara-C DNR/ara-C	124 ¹ 125 ¹	40 39	14 31	¹ all pts >60; IDA arm: more CR after course I (p .02) and more early/toxic deaths (p .001)
GOELAM (59)	IDA/ara-C Rubidazone/ara-C	111 ¹ 112 ¹	78 81	14 14	¹ pt age 15-50; CR after course I in 93% in both arms
Wiernik et al (60)	IDA/ara-C DNR/ara-C	97 ¹ 111 ¹	70 59	6 20	¹ 40% of pts >60; IDA arm: higher CR rate in <50 (p .03); lower refractoriness (p .01); WBC count not affecting CR rate (p .01)
SECSG (61)	IDA/ara-C DNR/ara-C	105 ¹ 113 ¹	71 58	10 18	¹ about 50% >60; IDA arm: better CR rate (p .03) and lower refractoriness (p .05)
GOELAM (62)	IDA/ara-C Rubidazone/ara-C	110 ¹ 109 ¹	76 61	— —	¹ pt age 50-65; IDA arm: better CR rate (p .01)

dent hematological disorder or secondary AML. As regards poor risk categories and the elderly, however, the activity of some of these IDA-based regimens was worthy of note. An Intergroup non-randomized study is presently being con-

ducted in the United States using an IDA/ara-C induction regimen.⁵⁶ Randomized studies have been undertaken since the late 1980s to compare directly ara-C plus either IDA or DNR-containing regimens.⁵⁷⁻⁶² In these studies (Table 5), IDA

Table 6. ICE chemotherapy studies in adult AML.

Study (ref.)	ICE dosages (mg/m ² /d)	No. of pts	CR %	Refractory %	Notes
Genoa (63)	I 8 d 1-3 C 200 d 1-5 E 150 d 1-3	51 ¹	82	8	¹ age 15-70
German (64)	I 10 d 1-3 C 100 d 1-7 E 100 d 1-5 + G-CSF	53 ¹	44	32	¹ all pts high-risk with secondary or MDS/AML
Royal Marsden (65,66)	I 5 d 1-5 C 2g bd d 1-5 E 100 d 1-5	30 ¹	60 ²	7 ³	¹ includes secondary AML; ² after course I; ³ after course II (different)
ALSG (67)	I 12 d 1-3 C 100 d 1-7 or 3 g d 1,3,5,7 E 75 d 1-7	30	87	10	—
Bergamo Hosp. ¹	I 10 d 1-3 C 200 d 1-7 E 100 d 1-5 + G-CSF	13 ²	64	15	¹ personal data from ongoing SBH/BG/VI study; ² age 20-65, including secondary and MDS/AML
EBMT-EORTC-GIMEMA (68)	I 10 d 1,3,5 C 100 d 1-10 E 100 d 1-5	— ¹	— ¹	—	¹ results not available

was administered at 12 or 13 mg/m²/d and DNR at 45 or 50 mg/m²/d, each for three consecutive days. The GOELAM Group chose a different schedule with a higher cumulative dose, IDA 8 mg/m²/d for five days.^{59,62} We can only suppose that the biological effects were roughly equivalent at these dosages for both IDA and DNR.

Results from these trials, two of which enrolled exclusively elderly patients, showed a rather homogenous advantage for the IDA arm in terms of CR rate, rapidity to CR, reduction of refractory disease, and lack of influence of the circulating leukemic cell burden (Table 5). Toxicity during induction was comparable to the DNR arm, with the exception of the Italian GIMEMA study in the elderly,⁵⁸ which indicated greater myelotoxicity for the IDA regimen with more hypoplastic deaths.

ICE: idarubicin-cytarabine-etoposide

It is clear from the data reviewed that an ICE regimen could represent a step forward in the initial management of adults with AML. As a matter of fact, reports on ICE combinations have recently made their appearance in the medical literature,⁶³⁻⁶⁷ and it is quite obvious that other studies are being started by leading groups.⁶⁸ Early results from these studies are

summarized in Table 6. A greater patient accrual seems necessary before any useful comment can be drawn. Theoretically, ICE would be better than either '3+7'/DAT plus etoposide (due to IDA substituting for DNR improving CR rates) or IDA-based '3+7'/DAT (due to additional etoposide improving CR quality). Although this may be very hard to assess formally by a direct comparison with an IDA/ara-C regimen, owing to the already narrow margin of improvement that is allowed, ICE could seriously compete with traditional programs once its toxicity were deemed acceptable. Obviously, this concept refers to full-dose ICE, i.e. without significant dose reductions with respect to reference regimens (Tables 1-3). In one study, for instance, toxicity from ICE was low but cumulative IDA was 24 mg/m² and ara-C was given for five days instead of seven.⁶³ Although results were in the high range, reportedly better than in historical controls, this reduction makes a proper assessment difficult and, furthermore, it may not be necessary. Due to its strong myelosuppressive properties, IDA was sometimes used at 10 mg/m² per dose, representing a 16% reduction from 12 mg/m². The therapeutic meaning of this choice remains obscure, but it seems unlikely that any further reduction would not negatively influence the likelihood of response. An EBMT-EORTC-GIMEMA three-arm trial is currently

Table 7. Open issues with ICE.

<i>Issues</i>	<i>Comments</i>
1. Is ICE really better?	Requires randomized study versus IDA-type '3+7' without etoposide or '3+7' with etoposide: evaluation of CR rate and duration, toxicity, costs.
2. What is ICE exactly?	Reference ICE regimen does not exist: see Table 6 and below.
3. Which patients?	Is ICE applicable to the elderly AML patient population?
4. How much:	
IDA	Upper limit seems 12 mg/m ² /d d 1-3, cumulative toxicity may be high at higher dose level or using alternate-day schedule, efficacy probably lowers below 10 mg/m ² /d d 1-3.
ara-C	Standard, intermediate, or high-dose: to make comparisons easier, standard-dose option would seem better at present.
etoposide	ALSG dosage (75 mg/m ² /d d 1-7) or equivalent 100 mg/m ² /d d 1-5 represent starting dose levels. Is an increase warranted?
5. Additional GM/G-CSF?	Requires randomization versus no CSF arm: it could shorten pancytopenic period favoring use of higher ICE dosages.

examining the relative merits of ICE with IDA at 10 mg/m²/d, given on alternate days for three times, versus similar regimens containing mitoxantrone or DNR.⁶⁸ A dose reduction of this kind, intended to reduce myelotoxicity while preserving efficacy through very prolonged exposure time to idarubicin and its cytotoxic metabolite IDA-ol, might cause unwanted or unexpected toxicity. In a different therapeutic setting, the alternate-day schedule was associated with intolerable marrow toxicity.⁶⁹ In a preliminary ALSG study ara-C was employed at high doses, but the results were no different.⁶⁷

The challenge

Altogether, results from the first ICE studies in adult AML are encouraging in terms of response and regimen-related toxicity, indicating the need for other confirmatory prospective studies. Currently, we trust that ICE is at least as therapeutically valid and nearly as toxic as historical programs, and there is justified hope it could be better. There is evidence that the control arms from some IDA-based studies yielded rather low CR rates, for reasons we still do not know but that should be elucidated. If this finding is not due to some as yet undetermined bias, but truly reflects a balanced prevalence of bad risk cases in both arms, then the results from IDA studies would be even more significant. It is a fact that IDA is much more expensive than DNR, raising the issue of a cost-effectiveness analysis. Finally, we have no sure data regarding the optimal timing and dosages of the ICE components, and very little information about the extent to which the addition of G/GM-CSF might modify the response to ICE and ICE-related toxicity.

There is some evidence indicating that IDA-based regimens have considerable activity in elderly AML, although treatment toxicity may be increased.⁵⁸ The additional use of GM-CSF in one uncontrolled study was associated with a better outcome, presumably through a reduction of marrow toxicity and pancytopenic deaths.⁵¹ The activity and toxicity of ICE regimens in the older patient population is not yet known. It is possible, as suggested by the Aus-

tralian randomized trial,³⁵ that etoposide could be relatively ineffective in this subgroup. Altogether, much more data need to be collected in this direction.

Far from being limitations, those listed above are the usual terms of acute leukemia therapy calling for well-designed protocols to be evaluated in properly conducted clinical trials (Table 7). This survey does support the view that ICE cannot be ignored by all those who are actively involved in the management of adult AML. It is our duty to give ICE a final shape, and to assess whether it is a worthy substitute for the time-honored '3+7' and DAT programs.

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