review
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THE USE OF ANTHRACYCLINES IN ADULT ACUTE LYMPHOBLASTIC LEUKEMIA

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ABSTRACT

A critical review of the role of anthracyclines in the management of adult patients with acute lymphoblastic leukemia was performed to define current indications for their use. Major pertinent clinical series were reviewed with reference to anthracycline type, cumulative dosage and dose intensity, and administration schedule during both induction therapy and postremission consolidation, comparing results, whenever possible, with non-anthracycline treatment groups. A subgroup analysis was performed to evidentiate disease subtypes likely associated with a favorable outcome to anthracycline treatment. The results indicated that anthracyclines may still play a primary role in this setting. In particular, anthracyclines should be used at full therapeutic doses, especially during induction and early consolidation; idarubicin could be a better choice than daunorubicin or adriamycin; finally, an early brief intensive treatment with anthracyclines may provide an excellent probability of long-term disease-free survival in CD10$^+$ t(9;22)-negative B-precursor adult ALL, obviating the need for prolonged maintenance or late reinduction therapy.

Key words: ALL therapy, anthracyclines

Progress and stagnation

Almost thirty years ago it became evident that a complete remission (CR) could be obtained and maintained for some time in many adult patients with acute lymphoblastic leukemia (ALL) who received moderately intensive multi-agent chemotherapy. When treatment principles, mostly derived from experience with childhood disease, were in better focus,[1-3] it was shown that up to twenty per cent of affected subjects could be cured. Next came a period of stagnation, which continues to the present day. All subsequent therapeutic attempts have substantially failed to improve upon historical results, particularly in relation to the ever increasing intensity, toxicity, and duration of current therapy. Only our understanding of the biological heterogeneity of the disease has made great advances, leading to more complete knowledge about prognostic determinants and hope for innovative forms of treatment.[4-6]

Strict adherence to the fundamental principles of chemotherapy is still the necessary pathway for attaining the best survival possible, especially within risk-adapted therapy programs.[7,8] Antineoplastic agents are most effective when used at the full therapeutic doses determined in phase I/II clinical trials and delivered as early as possible when drug resistance is less likely to develop.[9]

Practically speaking, if patients are to go through months or years of intensive, toxic, and subjectively unpleasant chemotherapy with a limited probability of success, we should always know how best to handle each drug at each treatment step.

The multiplicity and complexity of current treatment programs contrast with these reflections. At present there is neither a standard induction protocol nor agreement upon the best postremissional conduct, so that the limited repertoire of active antileukemic agents is very heterogeneously applied as far as drug choice, dosage and scheduling is concerned.

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The anthracycline problem

The crucial question of how best to use antileukemic drugs applies very well to a class of powerful and widely employed antileukemic agents, the anthracyclines (ANT).[10] ANT are routinely utilized in the management of adult ALL, yet there is no agreement on whether, when, how, or how much of these drugs should be given. Furthermore, the four compounds tested in Western countries: DNR, ADR, rubidazone (RZ, mostly in France) and idarubicin (IDA) have different toxicity, cost, pharmacokinetics and cytotoxicity. Finally, it is totally unknown whether any of these four drugs or ANT as a whole exert a preferential activity on specific subsets of ALL.

The review: aims and methods

The present review is intended as a first rational attempt at defining the role of and indications for ANT therapy in adult ALL. The extensive bibliography from recent review articles served as a basis for identifying pertinent, major chemotherapy studies.[5-8] These and other articles or relevant abstract reports were included provided they were sufficiently detailed about ANT and other drug types, dosages, timing, and long-term patient outcome (minimum 3 years), and clearly separated remission induction from postremission treatment phases. Because most of these studies were open, uncontrolled, involved several different drugs given in different ways, and adopted different criteria regarding patient selection and data presentation, a meta-analytical approach was felt to be inappropriate at this stage.[11]

Since the dose-time relationship is essential in cancer chemotherapy,[9] an attempt was made to correlate ANT dose intensity (DI) with clinical outcome. DI was calculated in each study as the ratio between the cumulative ANT dose (mg/m^2) and the duration of a stated chemotherapy phase (weeks). DI was arbitrarily calculated twice: during the first three months (12 weeks) of chemotherapy, including the induction phase as suggested by a recent article,[12] and over the remaining consolidation-maintenance period. Results were expressed as planned DI and not actually delivered DI, unless indicated otherwise. For comparative purposes, the incidence of late CR and refractory disease was determined. Late CR was defined as a response obtained beyond the first month of chemotherapy.

Finally, to lend further support to some of the hypotheses generated by this survey, we reviewed our personal experience with 229 adult ALL patients treated over the past 15 years in four consecutive collaborative trials.[13-20]

Induction of response

In patients with newly diagnosed ALL, the complete response (CR) rate to single-agent induction with ANT was 20%-58% (reviewed in refs. 21 and 22), unquestionable evidence that DNR, ADR, and RZ are truly effective anti-ALL agents. Subsequent to early monotherapy studies, both DNR and ADR were incorporated into standard VP(A) (vincristine and prednisone±asparaginase) regimens for both adult and childhood ALL.[1] Although the induction results were not much different in children, the superiority of a DNR-containing schedule was demonstrated in adults, where it increased the initial response rate from about 50% to 70% or more. In particular, a randomized CALGB trial was to become the key reference responsible for the addition of ANT to VP(A) in most of the subsequent European and North American programs.[23] The design of these studies was however heterogeneous (Table 1): the single randomized trial was from CALGB;[23] two others compared retrospective data;[24,25] and three more, including a recent study from Johns Hopkins University, exploited the sequential use of DNR in patients unresponsive to VP combinations.[26-28] Only in the retrospective study from Hôpital Saint Louis were induction results not improved by adding ANT.[25]

At the same time, three uncontrolled trials demonstrated beyond a doubt that ANT were not necessary for attaining a CR in up to 80% of cases if methotrexate (M) was added to VP(A) (Table 2).[29-33] Notably, the median time to CR was 48 days in the original MOAD report[31] and one month in the recent update,[32] a longer interval than in comparable ANT studies. The

Table 1. Complete remission (CR) rates with non-anthracycline vs anthracycline-containing combinations in adult ALL.

Group, year (ref.)	*No. of pts (median age)*	*Anthracyclines (mg/m²/d)*	*Days*	*Other drugs**	*CR (%)*
		Randomized trial			
CALGB, '84 (23)	53 (36)	–	–	V, P, A	47
	124 (32)	DNR (45)	1-3	V, P, A	78 (p=0.003)
		Retrospective trials			
Bart's, '78 (24)	32 (>14)	–	–	V, P	47
	51 (27)	ADR (30)	1, 15	V, P, A	71 (p=0.05)
Saint-Louis, '78 (25)	39 (>15)	–	–	V, P	79
	94 (>15)	DNR (NR)	weekly	V, P, ± C/A	74
		Sequential anthracycline trials			
Leiden, '75 (26)	41 (19)	–	–	V, P, ± A/Ac	46
	21 (17)	DNR (60)	weekly x 2,3	V, P	37 (total 83)
CALGB, '79 (27)	149 (37)	–	–	V, P, A	58
	33 (NR)	DNR (45)	weekly x 4		14 (total 72)
Johns Hopkins, '93 (28)	86 (32)	–	–	V, P, ± E/A	27
	63 (NR)	DNR (45)	22–24, 29–31	Ac	44 (total 71)

**V, vincristine; P, prednisone; A, asparaginase; Ac, ara–C; C, cyclophosphamide; E, etoposide. NR, not reported.*

UKALL Group conducted a large randomized trial that directly compared DNR and M during induction.[34] Although overall results were similar, it was confirmed that time to CR was significantly shorter for DNR-treated patients (Table 3). These observations indicate a more rapid inhibition of ALL cell growth by ANT compared to M, and this may be prognostically advantageous since in some studies patients who achieved CR beyond day 28 qualified as high-risk.[7] The review of toxicity between ANT and M regimens did not reveal any difference, but administering ANT may be easier since it does not require such a close monitoring of fluid balance and kidney function as with M.

Precise indications about optimal dosage, administration schedule, and preferable drug are largely undetermined for inductive therapy with ANT. Randomized studies addressing these key questions were very seldomly performed or were of limited interest. What is known is that both mitoxantrone (Mit), an antracenedione derivative, and RZ are equipotent substitutes for DNR, and that DNR at 45 mg/m²/dose was better than at 60 mg/m² because it was less toxic (Table 3).[35-37] An interesting trial from Mexico compared the effects of a classical CALGB-type three-day schedule (TDS) versus weekly (W) DNR. Results were not statistically different, but in the more intensive TDS arm there were more remissions and leukemia-free survival was also improved.[38] IDA was evaluated in two independent trials, both using a TDS.[18-20,39] These studies were of particular interest since IDA was consistently better than DNR in randomized trials conducted in adult acute myeloid leukemia (AML).[40-42]

Because of extreme hematologic and extrahematologic toxicity, results from both studies were disappointingly poor when the highest cumulative dosage of 36 mg/m² was given, but they improved considerably when this was reduced to 20 mg/m² (Table 3). A preliminary comparison with the previous ADR-based pro-

Table 2. Complete remission (CR) rates with methotrexate-containing, anthracycline-free combinations in adult ALL.

Group, year (ref.)	*No. of pts (median age)*	*Drugs**	*CR (%) total:late*	*refractory*
SECSG, '85 (29,30)	99 (23)	M, V, P	80:66	12
New York, '93 (31,32)	55 (38)	M, V, A, Dx	76:50	NR
SECSG, '92 (33)	192 (34)	M, V, P	60:37	NR

**M, methotrexate; V, vincristine; P, prednisone; A, asparaginase; Dx, dexamethasone. NR, not reported.*

Table 3. Complete remission (CR) rates from comparative anthracycline-based studies in adult ALL.

Group, year (ref.)	*No. of pts (median age)*	*Anthracyclines (mg/m²/d)*	*Days*	*Other drugs**	*CR (%)*
		Comparing ANT vs other drugs			
CALGB, '91 (35)	82 (31)	DNR (45)	1-3	V, P, M	65
	82 (32)	Mit (10)	1-3	V, P, M	63 (p=ns)
UKALL, '93 (34)	132 (NR)	M (500)	x3	V, P, A, MP	88
	134 (NR)	D (45)	1, 22, 36	V, P, A, MP	86 (shorter time to CR: p=0.04)
		Comparing different ANT, dosage or treatment schedule			
ECOG, '92 (36)	125 (32)	DNR (60)	1-3	Ac, TG, V, P	56
	122 (35)	DNR (45)	1-3	V, P	70 (p=ns)
FGTAALL, '93 (37)	284 (NR)	DNR (50)	1-3	C, V, P	78
	288 (NR)	RZ (100)	1-3	C, V, P	74 (p=ns)
Mexico, '93 (38)	44 (25)	ADR (20)	weekly x6	V, P	70
	48 (25)	ADR (30)	1-3	V, P	81 (p=ns)
IVAP,° '93 (18-20)	16 (36)	IDA (12)	2-4	V, P, A	44
	66 (36)	IDA (10)	2,3	V, P, A	91 (p<0.05)

**V, vincristine; P, prednisone; A, asparaginase; Mit, mitoxantrone; C, cyclophosphamide; Ac, ara-C; M, methotrexate; MP, mercaptopurine; TG, thioguanine*
°nonrandomized study comparing sequential treatment modifications.
ns, nonsignificant p value. NR, not reported.

tocol revealed a decreased incidence of late responders and of primarily refractory disease (p=0.01) in the IDA-treated group,[18-20] similarly to what was observed in AML studies. Considering the prolonged plasma half-life of IDA and of its cytotoxic metabolite idarubicinol (IDA-ol),[43] a two-day IDA schedule appears superimposable on a TDS with other ANT.

In a subsequent step we analyzed the bulk of results from other open studies with reference to ANT type, dosage, and schedule (Table 4)[12,16,17,36,39,44-68] Results were roughly superimposable: weekly or alternate week DNR/ADR, CR rates 71-87% (>80% in 3/11 studies), 12-49% of which occurred late, and incidence of refractory disease 11-27% (>10% in all 7 evaluable studies). With TDS or other intermediate-intensity DNR/ADR schedules the probability of CR was apparently in the same range (68-95%), but slightly higher when expressed in a different way (>80% in 8/17 studies). The incidence of late responses was usually below 10% when ANT were administered during the first few days of chemotherapy, and rose above 20% when ANT were started later on,[55,60] or when the total cumulative ADR dose did not exceed 50 mg/m².[67] With the more intensive TDS the frequency of refractory ALL was generally lower (1-18%, >10% in 7/13 evaluable studies); overall treatment results more or less repeated those of the Mexican randomized study.[38] As shown earlier, the low response rate in TDS IDA trials was due to toxicity problems rather than resistant ALL.[39]

Post-remission therapy

The impact of ANT on postremissional outcome was examined in relation to drug type, DI, and ALL prognostic subgroups. In uncontrolled ANT-free trials (Table 5)[23,27,29-33,55,64] the median CR length was generally less than 2 years, the probability of maintaining a long-term remission was 30% or lower, and the frequency of early relapses within the first year went as high as 50%, e.g. in the MOAD study.[32] Although survival rates were generally better in patients receiving additional ANT, it was not possible to determine with certainty whether this effect was specifically related to ANT or more broadly due to an overall intensification of multi-agent treatment plans. Three retrospective studies indicated a positive effect for ANT, which in one of them could be clearly

Table 4. Complete remission (CR) rates with anthracycline-containing combinations in adult ALL.

Group, year (ref.)	*No. of pts (median age)*	*Anthracyclines (mg/m²/d)*	*Days*	*Associated drugs**	*CR (%) total:late*	*refractory*
		Weekly/alternate week schedule				
Pavia, '82 (44)	62 (23)	DNR (60)	weekly x 6	V, P	72:40	27
Madrid, '85 (45)	47 (21)	DNR (30)	weekly x 6-8	V, A, P	87:12	NR
GIMEMA, '89 (46)	358 (31)	DNR (40)	1, 8, 22	V, A, P	79:47	13
GATLA, '91 (47)	282 (29)	DNR (25)	1, 8, 15, 22	V,P,A,C,Ac,MP	79:NR	13
GIMEMA, '92 (48)	343 (27)	DNR (40)	1, 8, 15	V, P, A, ± C	84:49	11
GMALL, '93 (49)	937 (25-27)	DNR (25-45)	1, 8, 15, 22	P,V,A,C,Ac,MP	74:19	15
Newcastle, '88 (50,51)	49 (N/A)	ADR (30)	biweekly x 6	V, P, Ac	79:NR	NR
L+B+V, '92 (16,17)	305 (27)	ADR (30)	1, 15 (29, 42)	V, P, A	71:25	12
EORTC, '92 (52)	106 (27)	ADR (30)	8, 29, 43	P, V, ± Ac	74:NR	NR
Cape Town, '92 (53)	46 (23)	ADR (20)	1, 8, 15, 22	V, A, P	78:NR	17
Norway, '94 (54)	79 (27)	ADR (30)	8, 14, 22	V, P, A, C	82:NR	NR
		Three-day and other intensive schedule				
MSKCC, '76 (55)	22 (16)	DNR (60)	20, 21	V, P	78:35	9
Bay, '91 (56)	109 (25)	DNR (50)	1-3, (15, 29, 30)	V, P, A	88:7	6
Swedish ALL, '92 (57)	113 (38)	DNR (30)	1, 2, 15, 16	V, C, P, A	77:NR	NR
CALGB, '92 (58)	202 (32)	DNR (45)	1-3	C, V, P, A	82:NR	NR
ECOG, '92 (36)	89 (31)	DNR (45)	1-3	V, P, Ac	69:6	NR
Verona, '94 (12)	86 (33)	DNR (25)	1-3 (x 3)	V, P	79:NR	3
SAKK, '94 (59)	63 (27)	DNR (45)	1-3	V,P,M,A,Ac,E	81:NR	14
MSKCC, '85 (60)	127 (25)	ADR (20-30)	17-19,35	V, P, C	84:35	6
Iowa, '89 (61)	59 (37)	ADR (30)	1-3 (x 2)	V, P, A	75:NR	12
SWOG, '89 (62)	168 (28)	ADR (20-30)	17-19, 36	V,P,C	68:NR	14
MD Anderson, '90 (63)	105 (30)	ADR (12 mg CI)	1-4	V, Dx, C	84:24	12
JALSG, '92 (64)	117 (38)	ADR (20)	1, 2, 8, 15 (22)	V, P, C, A	81:NR	NR
Finnish ALL, '92 (65)	76 (39)	ADR (35)	1, 3	V,Ac,E,Dx,M	82:NR	3
Pavia, '92 (66)	87 (>15)	ADR (35)	1-3, 22	V, Dx, C	77:NR	18
MD Anderson, '93 (67)	63 (39)	ADR (50)	4	V,Dx,C,M,Ac,A	95:22	1
Japan, '94 (68)	166 (35)	ADR (20)	1-3, 15-17	V,P,±A	64:NR	14
MSKCC, '93 (39)	14 (38)	IDA (12)	2-4	V,P,Ac,C,M,A	64:NR	14

**V, vincristine; P, prednisone; A, asparaginase; C, cyclophosphamide; Ac, ara-C; Dx, dexamethasone M, methotrexate; MP, mercaptopurine; E, etoposide; CI, continuous infusion; NR, not reported.*

Table 5. Durability of complete remission (CR) in non-anthracycline based adult ALL studies.

Group, year (ref.)	*No. of pts in CR*	*Drugs**	*Median CR (mo)*	*% CR at 5 yrs*
MSKCC, '76 (55)	18	Ac, TG, A, V, B	30	27
CALGB, '79 (27)	107	M, MP, V, P	15	25
CALGB, '84 (23)	122	MP, M	13-18	25 (3 yr)
SECSG, '85 (29,30)	79	Ac, TG, P, A, V, MP, M	17	30 (4 yr)
JALSG, '92 (64)	95	E, Mit, A	NR	30
UKALL, '93 (34)	232	P, V, Ac, M, MP	22	25
New York, '93 (31,32)	42	M, A, V, Dx, MP	12+	33

**Ac, ara-C; TG, thioguanine; A, asparaginase; V, vincristine; B, BCNU; M, methotrexate; MP, mercaptopurine; P, prednisone; E, etoposide; Mit, mitoxantrone; Dx, dexamethasone*

related to the actual DI of DNR during the first months of chemotherapy (Table 6).[12,47,69]

Another CALGB study considering this very important question in a randomized fashion did not show any improvement in the ANT arm, in contrast with the above conclusions.[70] Three other randomized trials, none of which supported a positive effect for increased DI, compared DNR at two different dosages,[46] Mit as a partial substitute for DNR,[35] DNR with RZ, and found similar outcomes.[37]

However, in uncontrolled trials a median CR longer than 2 years with a 3- to 5-year CR projection above 35% was more commonly observed in patients given higher ANT dosages within a short time. As shown in Table 7, such results

Table 6. Durability of CR from retrospective and randomized adult ALL studies: analysis by postremissional ANT type and dose.

Group, year (ref.)	*No. of pts in CR*	*Anthracycline drug (mg/m²/d)**	*early:late DI°*	*Other drugs#*	*Median CR in months (% at 5 years)*
		Retrospective			
MRC, '86 (69)	27	–		M, MP, V, P	20 (18)
	27	DNR (150) ADR (400)	12.5-25: 4.8	id.	21 (38) (p=ns)
GATLA, '91 (47)	109	–	8.3@: 0	M, MP, V, P	10 (20)
	113	ADR (120)	18.3@: 0	id., Dx, Ac, A, C	28 (34) (p=0.001)
Verona, '94 (12)	35	DNR (≤175)**	<21**: 8.6	V, P, M, MP, A	14 (20)
	33	DNR (176-225)**	>21**: id.	id.	36 (41) (p<0.05)
		Randomized			
GIMEMA, '89 (46)	103	DNR (240)	10: 5.7	V, P, A, M, MP,	17.3 (22, 4 yr)
	108	DNR (120)	10: 3	Ac, T (id.)	16.7 (22, 4 yr)
CALGB, '91 (70)	77	–		M, MP, V	19.5 (29)
	74	DNR (225)	30: 0	id., Ac	19.5 (29)
CALGB, '91 (35)	53	DNR (270)	22.5: 8	M, Ac, A, MP	12 (20, 3 yr)
	51	DNR (135)	11: 8	id., Mit	11 (20, 3 yr)
FGTAALL, '93 (37)	154 (tot)	DNR (420)	35: 4.1	Ac, A, P, V, MP, M, B, C	20 (32, 3 yr)
		RZ (840)	70: 8	id.	20 (32, 3 yr)

**cumulative post-remission dose; °DI, dose intensity (mg/m²/treatment week). DI early (during the first 12 weeks of therapy including induction) and late (during the remaining postremission therapy). #M, methotrexate; MP, mercaptopurine; V, vincristine; P, prednisone; Dx, dexamethasone; A, asparaginase; Ac, ara-C; C, cyclophosphamide; Mit, mitoxantrone; B, BCNU. @including induction DNR. **actual delivered dose (ranges not given).*

were reported in 4 out of 5 studies with an early DI of 20 mg/m²/week or greater,[14,17,44,54,56,61] but similar findings were obtained in only 4 out of 12 trials in which DI was below that range.[15,16,24,33,36,48,49,53,60,62, 63,66,68,71]

Data from IDA-based programs are limited. CR duration was negatively affected by toxicity and treatment delay in one study,[39] whereas the IVAP Study Group using 96 mg/m² as total post-remissional IDA reported no significant difference in terms of results, hematologic toxicity, or intercycle time compared with historical controls receiving 300-360 mg/m² ADR.[13,14,17] This seems to suggest a rough correspondence between the two drugs and their respective dosages during the consolidation period.[18-20]

ANT and ALL subsets

In the past, suggestions that particular drugs could act preferentially on different ALL subtypes were formulated. T-ALL, for instance, was said to benefit greatly from the use of ara-C, cyclophosphamide, and perhaps podophyllotoxins.[7,56] Data are scanty about ANT. In a full-dose, short-term, ADR-delivering HOP-L trial, results were relatively poor in T-ALL patients and much better in non T-cell disease, but unfortunately expression of the CD10 (cALLA) antigen was not assayed in 40 out of 50 patients with B-cell precursor ALL.[61] In a recent study from Verona University Hospital responders given DNR > 175 mg/m² early on during treatment (mean dose not reported) fared very well, but a subgroup analysis of this kind was not performed.[12] In two other studies employing relatively little ADR (100-120 mg/m²), together with other drugs including high-dose ara-C, results were comparatively better in high-risk T-ALL cases than in standard-risk CD10⁺ ALL.[15,16,49] In studies including consolidation-maintenance with DNR/RZ at 300-420/840 mg/m² and/or ADR at 120-300 mg/m², respectively, good results were obtained in CD10⁺ patients without t(9;22) or BCR-ABL rearrangements.[17,37,56,58,63,72] Since t(9;22) can be found in 25-50% of adult ALL cases with a CD10⁺ early-B immunophenotype, and since this abnormality is known to carry an extremely high risk of relapse, assessment of this prognostic variable is mandatory

Table 7. Durability of CR from anthracycline-containing open adult ALL studies: analysis by anthracycline cumulative dose and dose intensity.

Group, year (ref.)	*No. of pts in CR*	*Anthracycline drug (mg/m²/d)**	*early:late DI°*	*Associated drugs#*	*Median CR in months (% at 5 years)*
		early DI >20 mg/m²			
Pavia, '82 (44)	45	DNR (360)	35: 5	M, MP, V, P	10.4 (20)
Bay, '91 (56)	96	DNR (400)	21: 12.5	V, P, A,T, Ac, M, MP	33 (42)
Iowa, '89 (61)	44	ADR (370)	20:3.3	V, P, M, MP, C, Dac, B	50 (53)
Bergamo, '93 (14,17)	97	ADR (300-350)	23.7-25.4:6.2-8.3	V, C, MP, M, +/-Ac/T	27 (39)
Norway, '94 (54)	65	DNR (150) ADR (270)	20: 2.5	Ac, TG, M, MP, V, P, C	NR (54)
		early DI <20 mg/m²			
GIMEMA, '92 (48)	288	DNR (120)	10:1.2	V, Mit, P, Ac,Dx, T, M, +/-C	19 (45, 3y)
MSKCC, '85 (60)	106	DNR (180) ADR (360)	7.5: 9.7	Ac, A, C, TG, M, V, MP, P, B, Dac	51 (45)
MD Anderson, '90 (63)	88	DNR (600) ADR (168)	9: 8.4	M, A, V, Ac P, MP,C, B, E	22 (34)
Barts, '86 (24,71)	44	ADR (60)	5: 0	V, M, MP	18 (27)
SWOG, '89 (62)	115	ADR (420)	7.5, 3	V, Ac, Tg, M, P, A, C, MP, Dac, B	23 (30)
L+B+V, '90/92 (15,16)	38	ADR (60)	5: 0	V, M, MP, Ac	25 (27)
Pavia, '92 (66)	67	ADR (35)	14.6: 0	A, Am, Mit, E, C	12 (35, 3yr)
Cape Town, '92 (53)	36	ADR (120)	10:0	V,P,A,M,MP,+/-A,Ac,C	28 (NR)
ECOG, '92 (36)	217	ADR (240-320)	14.6-18.3: 10-11.1	Ac, C, V, P, M, A	10 (13-26, 3 yr)
SECSG '92 (33)	116	ADR (300-450)	8.3:6-14	V ,P, C, M, MP +/-Ac	13.7 (NR)
GMALL, '93 (49)	696	ADR (100)	8.3-15@:7.1	MP,M,V, Dx,C,Ac,TG, +/-T	24-27 (35- 39)
Japan, '94 (68)	106	ADR (120)	17:0	V, C, M, MP, P	13-17 (24-31)

**cumulative post-remission dose. °dose intensity (mg/m²/treatment week); DI early (during the first 12 weeks of therapy including induction) and late (during the remaining postremission therapy) . #M, methotrexate; MP, mercaptopurine; V, vincristine; P, prednisone; A, asparaginase; Dx, dexamethasone; T, teniposide; Ac, ara-C; C, cyclophosphamide; B, BCNU; Dac, actinomycin D; E, etoposide; TG, thioguanine; Mit, mitoxantrone; Am, mAMSA. @DNR during induction NR, not reached.*

for defining exactly CD10⁺ ALL response to ANT therapy. Altogether, these data would indicate a preferential activity of ANT in adult CD10⁺ B-precursor ALL provided full doses are given in a relatively short time, particularly in the t(9;22)-negative subtype. Information regarding the early-B CD10-negative and B-ALL subtypes is lacking.

Because we have employed either ADR or IDA at variable dosages since 1979 in four consecutive collaborative trials, we were able to compare treatment results according to ALL subtype, ANT type and cumulative dose. These trials were particularly suited for evaluating the impact of an early DI since the administration of ANT and other consolidation drugs was to be completed within a few months of CR, followed by prolonged low-dose maintenance with mercaptopurine and M without reinduction courses (Table 8).[13-20] For the purposes of this analysis CR patients were divided into standard (ADR 120 mg/m²) and intensive (ADR 360-405 mg/m², IDA 116 mg/m²) ANT treatment groups, corresponding to low or high ANT DI rates. In this sense, no significant difference was noted in B-ALL, early-B CD10⁻ ALL and T-ALL subgroups (data not shown). On the contrary, early-B CD10⁺ cases receiving standard dose ANT did worse than those treated more intensively (Figure 1). The intensive ANT group could be further divided into cases with t(9;22)/BCR-ABL rearrangement and those without (positive = 16, negative = 29, unknown = 18). As shown in Figure 2, the probability of relapse-free survival at 3 years and beyond was around 70% for t(9;22)-negative patients receiving a high early DI.

Concluding remarks

The first objective of this review was to assess the general role of ANT in adult ALL, and the second was to highlight what, in relation to their use in specific situations, was associated with the most beneficial effects. Although the associative multi-drug design of modern treat-

Table 8. Adult ALL studies conducted at Bergamo Hospital according to anthracycline type and dosage.

Protocol (ref.):	*HEAV'D (12,13)*	*OPAL- HDaraC (14,15)*	*R-HEAV'D (16)*	*IVAP-2 (17-19)*
Date started	Feb, '79	Mar, '84	Nov, '88	Oct, '91
No. of participating Centers°	2	2	2	5
No. of patients	82	27	39	81
Anthracycline (total mg/m²)	ADR (405)	ADR (120)	ADR (360)	IDA (116)
Induction drugs*	ADR, V, P, A	ADR, V, P, A	ADR, V, P, A	IDA, V, P, A
Consolidation drugs* (duration, mos.)	ADR, V, C (3)	ADR, V, C, Ac (3)	ADR, V, C, T, Ac (6)	IDA, V, A, C, B, Mel, E, T, Ac (9)
Maintenance drugs* (duration, mos.)	M, MP (36)	M, MP (36)	M, MP (24)	M, MP (6-18)

*°this update. *V,vincristine; P, prednisone; A, asparaginase; C, cyclophosphamide; Ac, ara-C; T, teniposide; B, BCNU,; Mel, melphalan; E, etoposide; M, methotrexate; MP, mercaptopurine.*

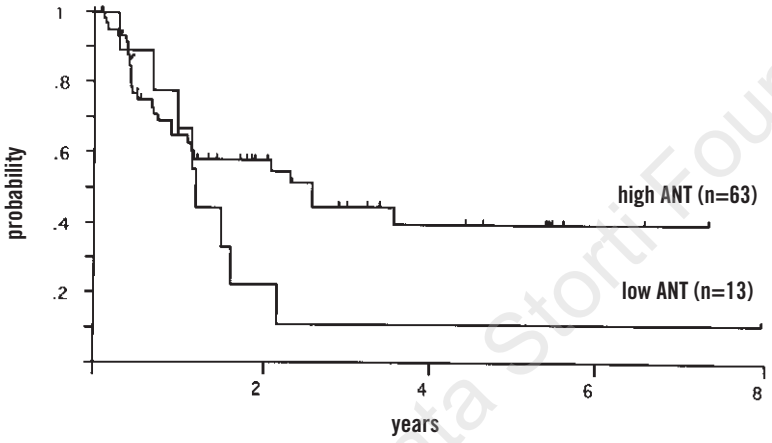

Figure 1. Kaplan-Meyer estimates of durability of first CR in CD10⁺ B-precursor ALL by anthracycline dose; p value from log-rank analysis is nonsignificant (>0.05). See text for details.

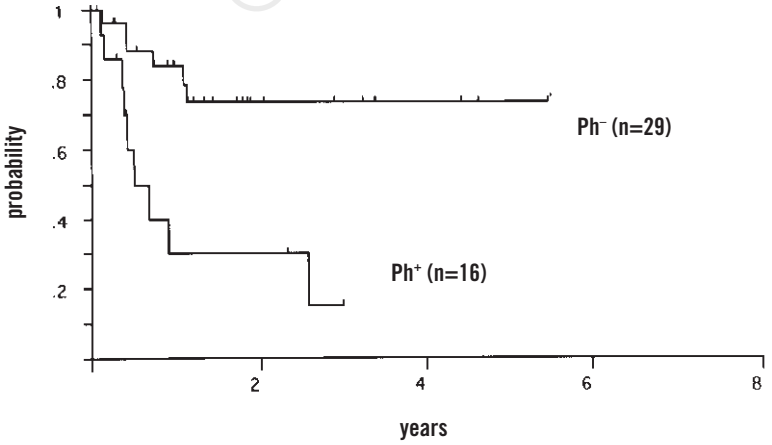

Figure 2. Kaplan-Meyer estimates of durability of first CR in intensive anthracycline CD10⁺ B-precursor ALL group by t(9;22)/BCR-ABL rearrangement; p value from log-rank analysis < 0.005.

ment programs is a serious limitation to assessing the merits of single drugs, we thought this effort worthwhile in view of the highly heterogeneous attitudes expressed towards ANT in recent years. The data reviewed herein indicate without question that ANT may play a central role in the optimal management of adult ALL. Since under certain circumstances this is a chemocurable disease, we should pay great attention to the rational utilization of these highly active agents. In a completely different perspective, cure was shown to be possible at somewhat inferior rates with programs totally excluding ANT, mostly centered around M.[29-33] This is only superficially a matter of contention. The real question is not – or not exclusively – whether one approach is better than another, but rather how to bring both to perfection and then assess their impact in specific risk groups.

Based on current evidence, ANT should be used at full doses during induction with VP(A) regimens and, when a doubt arises, they should be preferred to M. The latter, in a reciprocally advantageous manner, could be reserved for patients with absolute contraindications for ANT and *vice versa*. Furthermore, because both ANT and M are effective noncross-resistant drugs, a synergistic use was envisaged. When combined ANT-M induction therapy was attempted,[35,39,59,67] results ranged from very poor due to severe toxicity[39] to the best so far reported in adult ALL,[67] though a high level of supportive care was always required. Clearly this approach deserves further investigation, especially in predefined high-risk induction cases.

We found that the more intensive CALGB-type three-day schedule was associated with slightly better and quicker CR rates and lower incidence of refractory ALL. TDS is advantageous both conceptually and practically since the planned cumulative dose is delivered without reductions, whereas it is common practice at many centers to omit the third or fourth ANT injection in patients who are severely cytopenic or who develop infectious complications. Conversely, drug toxicity including myelosuppression, mucositis, and cardiac toxicity can be exacerbated.[73] While the latter is not a major problem during acute leukemia induction treatment, TDS requires a higher level of supportive care and, if other myelotoxic drugs (ara-C, cyclophosphamide, podophyllotoxin) are given jointly, this schedule might benefit from the association of granulocyte/monocyte colony stimulating factors (G/GM-CSF).[74]

In general terms DNR (45 mg/m^2/dose), ADR (30 mg/m^2/dose), and RZ (double the DNR dosage) appear to be roughly equivalent. A study with IDA demonstrated over two sequential steps that 12 mg/m^2/d for three days was too toxic, whereas 10 mg/m^2/d for two days plus VAP resulted in a CR rate of 90% with a negligible incidence of late responses and refractory disease.[18-20] These results closely resemble those observed in AML,[40-42] with the obvious difference of the drug dosage. Compared to other ANT, two interesting properties of IDA are the ability of its alcohol metabolite IDA-ol to cross the blood-brain barrier,[75] and a reduced vulnerability to some drug resistance mechanisms *in vitro*.[76-78] Due to the long plasma half-life of both the parent drug and its cytotoxic metabolite, which leads to accumulation upon repeated daily bolus administration (infusion-like effect), IDA would appear to be beneficial in B-ALL where exposure of rapidly cycling cells to cytotoxic drugs could be maintained for a relatively long time. Preliminary experience with the IVAP-2 protocol indicated a satisfactory response rate in B-ALL.[19,20] On the other hand, since IDA cytotoxicity is significantly stronger than other ANT on non-proliferating cells,[79] this compound should be considered even in ALL subtypes with a predominance of resting clonogenic cells. Currently there is no proof that these unique pharmacologic features will translate into an improved clinical outcome; nevertheless, the data presented here underscore the need for a more extensive evaluation of IDA and other new ANT[80] in adult ALL.

Substantial amounts of both DNR and ADR (or IDA) delivered precociously after CR were often associated with an excellent outcome, albeit not in all studies and unfortunately not in the single randomized one carried out.[70] The fact that these results were achieved without reaching levels usually associated with an increased risk of cardiotoxicity must be posi-

tively acknowledged. The threshold beyond which a positive ANT-related therapeutic effect became detectable was about 300-400 mg/m^2 for DNR, 200-300 mg/m^2 for ADR, and 100 mg/m^2 for IDA, respectively. Therefore the negative conclusions coming from the CALGB study could be explained in part by the lower cumulative planned DNR dose (225 mg/m^2).[70] Overall, the concept of an adequate early DI with ANT deserves attention in future studies.

The results analyzed by disease subtype point to an excellent prognosis for adult t(9;22)/BCR-ABL-negative (Philadelphia chromosome-negative, Ph$^-$) B-precursor CD10$^+$ ALL with intensive ANT treatment. The substantiating facts drawn from our studies[13-20] are: the limited duration of ANT-based consolidation; the strikingly different long-term outcome according to early ANT DI only, regardless of other drugs or prolonged low-dose maintenance; the early occurrence of most relapses, suggesting refractoriness to consolidation drugs, e.g. ANT, rather than maintenance; within this background, the very positive outcome of Ph$^-$ cases compared to the usual drug-resistant behavior of Ph$^+$ ones. The pharmacologic basis of ANT resistance in Ph$^+$ ALL is unknown. Because the most studied mechanism of multi-drug resistance (mdr-1) may be present in Ph$^+$ ALL,[81,82] a disease subset invariably associated with an ANT-resistant clinical pattern, the availability of ANT able to overcome the mdr-1 phenotype is not expected to be helpful in this setting.[76-78,80] It remains to be determined whether IDA plus other modifiers of the mdr-1 phenotype could improve results in other mdr-1$^+$ ALL subtypes.[83,84]

Our data are not in contrast with the previously expressed hypothesis of an apoptotic effect favored by maintenance chemotherapy in patients with B-precursor ALL,[85] rather they suggest that eradication of the disease can be obtained earlier in the Ph$^-$ CD10$^+$ subgroup by aggressive use of ANT, in keeping with prior demonstrations of chemocurability through brief intensive treatments in other B-cell neoplasms.[86,87]

In conclusion, ANT may still be effective in the optimal management of adult ALL, with specific applications in different treatment phases and disease subtypes. The issues highlighted in this review should be critically considered in new studies. Both clinical and pharmacological research should continue to work on the major obstacles of toxicity and drug resistance *in vivo*.

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