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STRATEGIES FOR THE TREATMENT OF RECURRENT ACUTE LYMPHOBLASTIC LEUKEMIA IN ADULTS

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ABSTRACT

Bone marrow recurrence of adult acute lymphoblastic leukemia is typically an aggressive and most often rapidly fatal condition, an ideal setting for testing the latest research developments and experimental therapeutic options. Here we review recurrence mechanisms and treatment possibilities in order to identify the most appropriate clinical conduct. Choice of retreatment drugs and their dosages, related or unrelated donor bone marrow transplants, autologous peripheral blood stem cell transplants, immune manipulations, reversal of drug resistance, and restoration of apoptosis are all part of an integrated short-term therapeutic and decisional network to be developed for specific patient and disease prognostic subgroups.

Key words: adult ALL: recurrence, management, new options

In this survey we discuss the role of all existing management options for adult recurrent acute lymphoblastic leukemia (ALL), from conventional chemotherapy to the latest research developments. The compelling reasons for tackling this subject are exemplified by the ever increasing number and complexity of reportedly effective therapies and the lack of a general consensus on specific retreatment phases and modalities. To facilitate the reader's understanding, we will first define the clinical and biological issues underlying the problem of recurrence (section 1), then analyze in detail known retreatment results by therapy type and intensity (section 2) and, finally, discuss the case and the indications for a revised strategy based on available traditional and investigational therapeutic weapons (section 3).

Nature of the problem

The relevant facts

ALL in people aged 15 to 60 years is chemocurable in approximately 20-30% of cases using moderately aggressive front-line treatments.[1] The therapeutic intervention is biphasic: a complete remission (CR) must be achieved first, and secondly, recurrence must be avoided. The concept of cure refers to a patient who is alive and well, leading a normal life, in first unmaintained remission five to ten years after ALL diagnosis. A recurrence beyond that point is rare though possible;[2] nonetheless, it seems impractical to extend beyond five years the minimum length of follow-up needed to declare a patient at great *risk* for cure. It is also possible that with modern highly intensive programs the frequency of late relapses will be reduced with respect to older trials, as was observed in a recent large French study in patients undergoing high-dose chemo-radiotherapy followed by either allogeneic or autologous bone marrow transplantation.[3]

Treatment failure is caused by either a primary refractory disease or, much more commonly, by a recurrence. Bone marrow relapse is the major reason for treatment failure. In a review we performed on the long-term outcome of 269 patients,[4] bone marrow relapse was by far the predominant adverse event affecting prognosis (Figure 1). Relapse in the central nervous sys-

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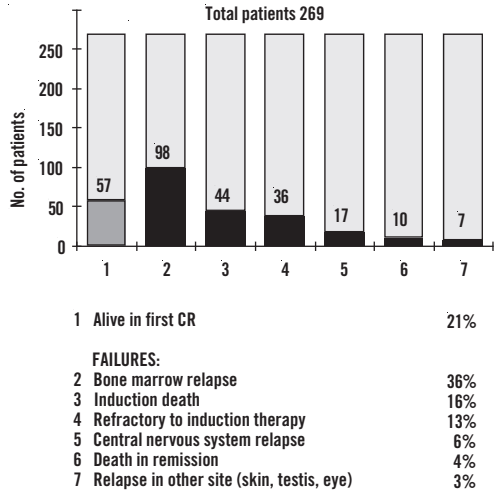

Figure 1. Outcome and reasons for failing front-line therapy in adult ALL (adapted from ref. #3). Failure is defined as death by any cause or recurrence in any site.

tem or in other sites, such as the testis, is now of less concern than in the past as a result of increasingly effective prophylactic measures and an overall intensification of treatments. Henceforth, we will refer only to bone marrow recurrence of adult ALL.

Risk factors

Many reasons for relapse have been identified. Higher recurrence rates have been variously associated with hyperleukocytosis >30-50 $\times 10^9$/L, advancing age, chromosomal aberrations [in particular t(9;22); t(4;11); t(8;14)], late achievement of CR, T-cell/pro-T-cell ($CD7^+$, E-rosette-negative) and pro-B-cell (null) immunophenotype, co-expression of myeloid antigens and the stem-cell CD34 antigen, FAB L2 and L3 morphology, and bulky or extramedullary disease.[1,3-12] Recent experience however suggests that previous high-risk situations may benefit from treatment intensification or drug tailoring, as in the case of T-ALL receiving early therapy with cyclophosphamide, cytarabine and podophyllotoxins.[1]

The first adverse prognostic factors (APF) to be recognized were almost exclusively clinical, and links with the intrinsic nature of the disease were ignored for a long while. A step forward came from the joint analysis of ALL cell immunophenotype, karyotype and gene rearrangement studies. By combining morphology, immunology and cytogenetic study results (MIC), discrete ALL entities having different clinical and prognostic behavior can now be identified.[13] The number and complexity of known APF make it very difficult to ascertain which of them is ultimately responsible for treatment failure in individual patients, but exceptions occur as with t(9;22)-positive ALL, which is invariably associated with ALL regrowth and chemotherapy failure.

Lately, interest in prognostic factors and recurrence-related problems has been revived by new insights. For the sake of clarity and brevity, we will refer solely to those conceptual and research developments for which clinical application is foreseeable within a reasonable lapse of time in a sufficiently large patient population.

First, ALL diagnostic features, namely the immunophenotype and cytogenetic profile, have been documented to change from presentation to relapse in some cases,[14,15] in line with the hypothesis of clonal evolution towards a more aggressive disease. This issue is still much less understood in adult ALL than in the childhood disease.[16,17] Sometime the phenotypic shift involves a totally different, drug-related secondary leukemia rather than a clonal evolution at relapse.[17] It is unknown whether indications for and response to retreatment may differ from the others in ALL cases undergoing a phenotypic shift at relapse. Exact identification of the leukemic clone at relapse is clinically relevant in order to select the most appropriate salvage treatment and to obtain useful information for subsequent monitoring of the disease. Methodologic options for detecting and monitoring minimal residual disease (MRD) include conventional cytogenetic techniques, fluorescence *in situ* hybridization (FISH), flow cytometry, polymerase chain reaction (PCR) on genetic abnormalities or gene rearrangements, and colony assays.[18] Although the practical value of these techniques is presently undetermined and limitations exist regarding methodologic aspects and sensitivity levels, MRD research is expected to help unravel the biology of persistent disease,

the mechanisms and timing of recurrence, and eventually to have a positive impact on therapeutic choices. A novel and potentially very useful tool for predicting early relapse was recently described.[19] Mice with severe combined immunodeficiency (SCID) were inoculated with leukemic cells from high-risk B-lineage ALL patients. Spontaneous ALL growth in SCID mice was significantly associated with a high risk of relapse (64%) and low 5-year event-free survival (29%) in the patients, whereas recurrence was noted in only one out of 19 patients (5%) whose ALL cells did not cause histopathologically detectable leukemia in SCID mice.

Second, besides traditional host- and disease-related APF, reduced application of chemotherapy programs and undue reductions of stated dose intensities for some drugs were shown to facilitate recurrence.[20-22] Despite the fact that this risk has been underscored by undisputed authorities in the past,[23] it has all too often been ignored due to a lack of self-criticism.

Third, the interactions between minimal residual disease and host immunocompetent cells, namely spontaneously non-HLA-restricted cytotoxic cells, are now better understood. These cytotoxic cells can be activated and expanded *in vitro* as well as *in vivo*, principally by interleukin-2 (IL-2).[24] Pathogenetic links have been postulated between recurrence (progression) and inadequate cytotoxic response in the host. It is still not known whether artificially enhanced lymphokine-activated-killer cell (LAK) activity could be a valid adjunct to classical chemotherapy in adult ALL.[25]

Apoptosis and drug resistance

Other new lines of research involve apoptosis and drug resistance studies. Apoptosis, or programmed cell death,[26] is altered in many human neoplasms, including leukemias, in relation to dysregulated expression of one or more of the cellular genes involved. Reduced apoptosis confers a survival advantage on the neoplastic cell population. As specifically regards ALL, an apoptotic-like mechanism was suggested to facilitate the clearing of residual ALL cells in patients receiving continuous low-dose standard maintenance.[27,28] Recently, mutations in the apoptosis-related p53 gene have frequently been detected in Burkitt-type ALL at presentation[29] and in relapsing T-ALL refractory to salvage chemotherapy,[30] whereas overexpression of the bcl-2 gene has been found to be associated with glucocorticoid-dependent apoptosis resistance in lymphoid cell lines.[31]

Attempts at restoring altered apoptosis were initiated with antisense BCR-ABL oligonucleotides in a Philadelphia chromosome-positive lymphoid cell line,[32] and with interleukin-4 (IL-4) in high-risk ALL cells cultured *in vitro*.[33] The preliminary experimental and clinical background certainly warrants further study in recurrent disease.

The observation that most chemotherapeutic agents may work through induction of apoptosis raises the strictly related problem of drug resistance. Several types of drug resistance to current anti-ALL drugs have been described,[34] which were sometimes found to prevail at or to predict relapse. The most studied mechanism of P-glycoprotein (Pgp)-mediated multi-drug resistance (MDR) (*mdr-1* phenotype)[35-38] is under re-assessment because of the serious technical pitfalls concerning its histochemical demonstration and also because other important mechanisms are being elucidated: MDR-associated protein (MRP), LRP, topoisomerase II/I, glutathione S-transferase.[38-40] It has been suggested that p53 gene mutations and overexpression of the bcl-2 gene could eventually account for true MDR in human tumors, including leukemias.[40,41] For practical purposes, *in vitro* documentation of drug-resistance should rely on a functional laboratory test that encompasses all the existing pathogenetic possibilities and possibly reflects or predicts the clinical behavior of the disease. Both MTT and DiSC are short-term functional assays able to quantify the degree of cell growth inhibition inducible by drugs, regardless of the underlying drug-resistance mechanism, and have been tested with some success in childhood ALL.[42-44] The major obstacle with these assays is represented by the difficulty in maintaining ALL cells in a proliferative state *in vitro*. There is virtually no information concerning MTT/DiSC predictive power in adult ALL clinical studies. Direct

assessment of the subcellular distribution and DNA incorporation of drugs could be another complementary way for the pretreatment identification of drug resistance. This possibility has already been exploited with anthracyclines and Ara-C in acute myeloid leukemia (AML).[45,46]

Overcoming drug-resistance is under active scrutiny at many Institutions. Although this strategy is still in its infancy and evaluation of clinical toxicity is in an early phase, encouraging results have been reported, almost exclusively in poor-risk AML, using inhibitors of Pgp-mediated anticancer drug transport and metabolic signal transducers, such as verapamil, cyclosporin-A, cremophor EL and staurosporine,[47-49] or with drugs affecting topoisomerase II, topoisomerase I, and other non-Pgp-mediated MDR mechanisms.[34,50] Interestingly, in one study cyclosporin A enhanced the effects of an anti-CD5 ricin A-chain immunotoxin against a T-lymphoblastic cell line.[51] The problem of drug resistance and its reversal by modulators needs to be worked out entirely in recurrent ALL.

A literature overview

Aims and methods

Obtaining detailed knowledge from past experience is a necessary step towards the identification of the best retreatment strategy. Although recurrence may eventually concern about 60% of all patients obtaining a CR, retreatment of adult ALL has not attracted great interest in the recent medical literature, probably because of the shortage of active anti-ALL drugs and the uniform paucity of results. The most recent review article, reporting on 41 trials published up to 1992, focused mainly on the second remission induction phase.[52] Here we consider 58 total reports in the form of full papers or sufficiently detailed abstracts that consider remission reinduction and consolidative treatment phases separately.[53-110] This is not a meta-analysis because of the heterogeneous criteria adopted in these reports with regard to patient selection, demographic features, disease stage, study definitions and data presentation. Only adults aged 15 years and older who initially relapsed in the bone marrow were considered. Primarily refractory patients, second or third recurrences, children, extramedullary relapses, and AML cases from studies on both AML and ALL were excluded whenever possible. The percentage of pediatric cases present in some key references was reported. To highlight response-oriented treatment principles, data analysis and statistical comparisons were made between groups rather than single studies. The guidelines used for selecting retreatment groups included drug number (one, two, three or more drugs, excluding corticosteroids, that were adopted by almost all programs), type (anthracyclines, mitoxantrone, acridinyl anisidide or AMSA, alkylating agents, anti-metabolites, plant alkaloids, other agents) and dosage (conventional or high). Results of postremissional therapy were analyzed with reference to the following choices: none or not specified, conventional prolonged low-dose maintenance, reinduction or consolidation courses, any combination thereof, and allogeneic or autologous bone marrow/blood stem cell transplant (BMT/BSC) procedures. Response rates were compared using the chi-squared test with Yate's corrections.

Remission reinduction

Response to reinduction programs varied widely. Overall, the principle was established that *more* was *better*, and that some drugs or drug combinations were superior to others (Table 1). Conventional-dose single-agent treatments, essentially with anthracycline-like drugs, resulted in a rather low probability of success, which improved considerably (up to 50% overall) when other agents were added. In this context the activities of idarubicin, mitoxantrone and AMSA were roughly superimposable. A carboplatin-etoposide combination was ineffective in a small patient group.[74] Results with high-dose therapy using alkylating agents were similar to conventional-dose therapy, whatever the drug combination. Because high-dose regimens were mainly based on high-dose Ara-C, the role of this drug was examined in detail. With single-agent high-dose Ara-C, response was only 28% and was not increased by the addition of L-asparaginase; however, all

*Retreatment drugs**	*# of studies (total # of pts)*	*CR # (%)*	*p-value°*	*References*
Conventional dose, by drug type and number				
ANT monotherapy	7 (81)	20 (25)	—	53-59
ANT in association	10 (183)	87 (47)	0.0001	54,60-68
Association without ANT	6 (110)	47 (43)	0.007 (NS)	69-74
Any two drugs	9 (119)	47 (39)	0.02 (NS)	54,60,62, 67-69,71, 72,74
Three or more drugs	7 (174)	87 (50)	0.0000 (0.002)	61,63-66,70,73
High-dose, by drug type and number				
Alkylating agents (± other)	4 (54)	25 (46)	ND	69,75-77
Ara-C: monotherapy	10 (106)	30 (28)	—	78-87
+ASP	2 (20)	6 (30)	NS	88,89
+VCR/POD	3 (32)	16 (50)	0.02	87,90,91
+ANT	3 (81)	40 (49)	0.009	92-94
+MTN	8 (130)	62 (48)	0.003	95-102
+AMSA	4 (62)	36 (58)	0.0002	103-106
+two or more drugs	4 (117)	77 (66)	0.0000	107-110
Any one drug	11 (109)	32 (29)	—	73,75-84
Any two drugs	22 (364)	177 (48)	0.0001	72,74,84-103
Three or more drugs	5 (128)	83 (65)	0.0000 (0.002)	66,104-107
High-dose Ara-C+				
any one drug	20 (324)	160 (49)	0.0002	84-103
any two or more drugs	4 (117)	77 (66)	0.0000 (0.003)	104-110

Table 1. Reinduction results by drug type, dosage, and number.

Legend.
**ANT, anthracyclines (including AMSA and mitoxantrone if not otherwise specified); Ara-C, cytosine arabinoside; ASP, L-asparaginase; VCR, vincristine; POD, podophyllotoxins (etoposide and teniposide); AMSA, acridinyl anisidide; MTN, mitoxantrone. Prednisolone/prednisone were omitted because included in all studies at variable dosages.*
°reference group is marked –; figures in parentheses refer to comparison with immediately preceding group; ND, not done; NS, non significant p value.

other drugs added to high-dose Ara-C appeared to act synergically, improving this figure significantly. The best results, almost without exception, were obtained when two or three agents were added to intermediate/high-dose Ara-C. Additional drugs used were anthracyclines, mitoxantrone, AMSA, spindle venoms, and podophyllotoxins. Nonresponders died of either refractory ALL or pancytopenic complications. The incidence of treatment-related deaths correlated directly with retreatment intensity, and inversely with the antileukemic effectiveness of study combinations.

Postremission chemotherapy

Patients entering second or late CR were given a variety of postremission regimens and, whenever possible, were chosen for allogeneic BMT. Four postremission chemotherapy groups were identified: none or not reported; conventional maintenance using methotrexate and thiopurines or other unspecified drugs; short-term reinduction courses with induction-like drugs/regimens; variously intensive multi-drug consolidations with or without reinduction and maintenance pulses (Table 2). Apparently, CR durability was not significantly affected by type

Table 2. Postremission chemotherapy results.

*Treatment program**	*# of studies (total # of patients)*	*CR range (mos.)*	*Survival range (mos.)*	*References*
None/not specified	12 (176)	2-10	2-14	43,56, 62,63,68,76,77,83, 90,95,96,106
Maintenance	6 (90)	3-8	3-9	54,60,61,75,89, 94
Reinduction	5 (76)	2-4.5	–	57,69,71,72,86
Consolidation ± reinduction ± maintenance	12 (277)	3-8	5-11	64,65,70,87,96,97,101,102, 104, 107,109,110

**In order of increasing intensity.*

or duration of postremission chemotherapy, so that longer disease-free intervals could not be clearly attributed to the most intensive or prolonged of the programs examined. However, it has to be emphasized that more aggressive retreatment regimes were generally reserved for patients failing recent, very intensive front-line programs, which presumably reflects a higher incidence of drug-resistant phenotypes and other APF. Long-term (two years and over) response rates with chemotherapy only were hardly above 10%, with a subsequent relapse occurring in the majority of patients after 3-6 months. The early finding that outcome was better when the prior remission lasted 18 months or longer was confirmed in some but not all studies, and might still represent a useful prognostic indicator. Remission inversion occurred when a remission longer than the previous one was achieved. The clinical meaning of inversion is potentially relevant but remains undetermined because of the lack of long-term updates in most of the studies.

Allogeneic bone marrow transplantation

Allogeneic BMT can induce durable remissions in relapsed adult ALL (Table 3). At present, this seems to be the only way a cure can be achieved in some patients. With allogeneic BMT, effective salvage was obtained in 10-45% of cases, the average current figure being 25-45% as recently reviewed.[125,126] In many of these reports the results obtained in children were not clearly separated from those of the adults. Results were generally better in second CR patients than in those with refractory disease or in late CR, confirming the importance of an adequate reduction of the leukemic burden before transplant. Partially matched related donor and matched unrelated donor (MUD) allogeneic BMT were also shown to offer survival possibilities,[127,128] though the success rate remains lower than with matched siblings. Patients relapsing after BMT can still undergo a second transplant, but again the probability of survival is reduced.[129] The crucial points about allogeneic BMT are that many patients do not have a suitable related marrow donor, that MUD are very infrequent, and that prompt patient referral to transplant centers may be delayed for a variety of reasons, e.g. unresolved infections, other medical contraindications, logistical problems. The risk of further recurrence increases greatly if BMT is performed beyond three months from achievement of remission.

Autologous bone marrow transplantation

To obviate in part the shortcomings relative to allogeneic BMT, an autologous source of hema-

Table 3. Allogeneic BMT results (minimum 20 patients).

Author, year (ref.)	*# of pts*	*% DFS at 3-5 years*	*Notes*
Dinsmore, '83 (111)	28	65	Percent children not reported
Blume, '85 (112)	30	46	Percent children not reported
Van Lint, '86 (113)	25	32	Including children
Herzig, '87 (114)	208	22	Age range 1-47 years (median 19)
Kersey, '87,'92 (115,116)	88	33	12% in 1st CR at high-risk, age 4-48 years (median 15)
Gratwhol, '88 (117)	442	34	Including BMT in 3rd/4th CR, age range 1-47 years (mean 18)
Barrett, '89 (118)	391	26	Age range 1-49 years (median 15)
Wingard '90 (119)	36	43	Including children
Doney, '91 (120)	48	10	Age range 18-50 years
Buckner, '92, (121)	192	12/15	Relapse/second or later CR, median age 23 years
Bortin, '92 (122)	420/921	23/38	At relapse/second or later CR
Copelan, '92 (123)	30	42-13	By risk group, age range 15-42 years (median 23)
Weyman, '93 (124)	63	42	12% in 1st CR, 70% < 16 years

CR: complete remission; DFS: disease-free survival.

topoietic stem cells was considered as an alternative means of supporting supra-lethal chemoradiotherapy. In most of these studies, the autologous marrow harvest underwent *ex vivo* immunological or pharmacological manipulations in order to eliminate residual clonogenic ALL cells prior to *in vivo* reinfusion. These manipulations are technically cumbersome and lack standardization; moreover, there is no definite proof that they render the autologous graft leukemia-free. A good correlation between the pretrasplantation leukemic burden in the remission patient's bone marrow and clinical outcome was reported,[130] underscoring the need for effective consolidation treatment equivalent to *in vivo* purging before marrow collection. Results with purged autologous ABMT were intermediate between chemotherapy and allogeneic BMT studies (Table 4). In a recent and relatively large GIMEMA/AIEOP trial directly comparing chemotherapy and allogeneic or unpurged autologous BMT in a rather young patient population (median age 14 years), overall results were unsatisfactory regardless of the treatment arm and, specifically, there was no difference between chemotherapy and autologous BMT.[92]

Autologous blood stem cell transplant

Experience with autologous blood stem cells (BSC) in relapsed ALL patients is still anecdotal.[136] Early results were in the autologous BMT range, at least suggesting further exploitation of this strategy. The indications, principles and limits of BSC autotransplants in leukemia patients were recently reviewed.[137] The therapeutic value of this rapidly expanding technique as compared to that of autologous BMT is unknown, as is the very important issue of residual disease contamination of ABSC. Contrary to early thoughts, 1-2×10^6/kg $CD34^+$ BSC, or even less, may be enough to sustain an adequate hematological recovery in lymphoid malignancies,[138] perhaps reducing the risk of contamination. Exceptions to this may occur with heavily pretreated subjects.[139] In addition, ways of selecting definitely nonleukemic $CD34^+$ stem cells may soon be at hand for both marrow and BSC.[140]

Preliminary evidence from pilot studies in Philadelphia-positive ALL indicated that both bone marrow immunomagnetic purging and BSC collection may sometimes result in a decreased BCR-ABL rearrangement signal, as detected by the sensitive polymerase chain reaction, with respect to baseline and bone marrow.[141,142] A recent small trial confirmed the feasibility of this approach in this ALL subtype at recurrence, with one disease-free survivor at 18 months from among five initial responders.[143] Similar conclusions were drawn in childhood ALL when sensitive, prospective monitoring of gene rearrangements in peripheral blood leukocytes was employed.[144] Results in unselected adult patient series are awaited with interest for comparison with autologous BMT.

Table 4. Autologous BMT results (minimum 20 patients).

Author, year (ref)	*# of pts*	*% DFS at 3-5 years*	*In vitro purging**	*Notes*
Kersey, '87,'92 (115,116)	153	21	MoAb±4HC	12% in 1st CR at high-risk; age range 2-42 years (median 9)
Kantarjian, '89 (63)	64	8	–	% CR at 2 years
Rizzoli, '89 (131)	46	27	4HC	30% <15 years
Simonsson, '89 (132)	32	31	MoAb	% CR at 18 months, age range 3-25 years (median 9)
Soiffer, '93 (133)	21	20	MoAb	Only B-lineage ALL, age range 18-54 years (median 28)
Doney, '93 (134)	52	21	MoAb	At 2 years, age range 2-46 (median 15)
Sierra, '93 (135)	14/7	34/0	MoAb (75%)	2nd CR/beyond 2nd CR, including children
EBMTG, '94 (136)	471	31/37	MoAb±4HC (60%)	Standard/high risk, median age 30 years

*CR: complete remission; DFS: disease-free survival; *MoAb: monoclonal antibodies; 4HC, 4-hydroperoxycyclophosphamide*

Retreatment strategies

The case for a change

It is evident that reliance on traditional retreatment programs is an insufficient strategy for adults with recurrent ALL. We must be fully conscious that recent clinical and laboratory research is now allowing us to explore highly innovative approaches, and the current challenge is to improve patient outcome by merging part of the old with the new. Having reviewed all available therapeutic techniques, we now wish to translate this knowledge into a series of proposals for future studies. Although this is a personal view, we urge moving from long-held positions to a more critical use of traditional therapeutic tools and their close integration with advances resulting from biological research. We also believe that significant progress can only follow refinements and improvements in all retreatment components, none excluded. This target is illustrated below in the context of patient possibilities and needs.

General outlines

Recurrent ALL is a clinical emergency for the following reasons: high cumulative incidence of APF, prior intensive treatment and related toxicity, high prevalence of drug resistance patterns, and lack of truly effective remission consolidation treatments. Although the second remission rate may still be high, response is invariably short-lived, and long-term salvage is thus far achievable only with an allogeneic BMT. Since many patients lack a BM family donor, or are at great risk of further recurrence before BMT is carried out, or cannot undergo BMT because they are too ill, the positive impact of the procedure on the whole population at risk is at best limited.[145]

As a matter of fact, retreating ALL with curative intent is not always worthwhile; different situations probably deserve different approaches. A general overview of the problem is presented in Figure 2. In older patients (>50 years) the risk of pancytopenic death during aggressive retreatment can be extremely high, and the overall prognosis remains very poor if there is no family donor for allogeneic BMT or, more commonly, if BMT is not even considered due to the patient's age. For some of these cases, palliative ambulatory care with steroids, transfusions and vincristine injections or oral mercaptopurine, as clinically indicated, may at present be a sensible choice for prolonging survival and preserving an acceptable quality of life. These patients are also candidates for nonconventional therapeutic trials at qualified centers. This requires careful explanation to the patient and the patient's relatives, informed signed

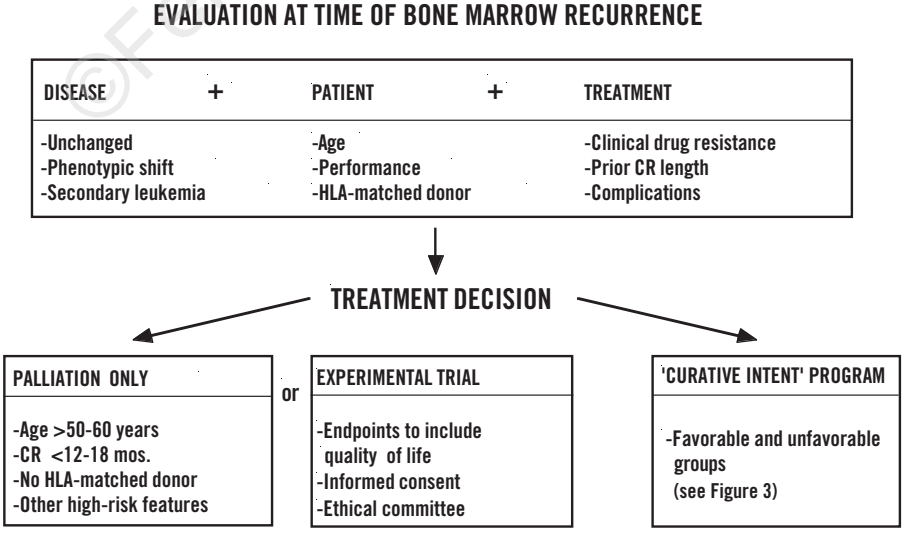

Figure 2. Clinical guidelines for bone marrow relapse of adult ALL.

consent, and protocol approval by an expert ethical committee.

Obtaining a response

If a patient is 50 years or younger, has a matched or partially mismatched family donor, and suffers from a recurrence after a prior CR that lasted longer than 12-18 months, reinduction must be attempted with a multi-drug regimen including intermediate/high-dose Ara-C (if not previously used). Remission rates in excess of 50% should be obtained. Great care must be devoted to avoiding opportunistic infections, especially invasive fungal infections, that might hamper the subsequent consolidation and BMT phases. The use of effective antibacterial and antifungal prophylaxis and of myeloid cell growth factors can lead to a decreased incidence and severity of these complications and their sequelae.[102] Selected cases with all low-risk features (age <30-35 years, low leukocyte count, no adverse cytogenetics) relapsing after long remissions (>18 months) may still have very good chances of getting a second CR with low to intermediate intensity regimens. These cases, when a marrow donor is present, can be considered for standard intensity treatment or even be retreated with the primary induction schedule to avoid the toxic side effects of investigational combinations.

The fact that in most instances alternative drugs should be used at recurrence is obvious, but there may be none if the front-line schedule, as frequently occurs with last generation programs, already included them all. Recently, a high-dose methotrexate- and Ara-C-containing drug combination followed by a short individualized folinic acid course proved effective in relapsed ALL of childhood.[146] Because of the very high drug dosage and the substantial toxicity reported in children, this program may not be easily applicable to adults for whom methotrexate is seldom prescribed at greater than 1.5 g/m^2 because of tolerability problems. In addition, a recent study indicated that methotrexate peak plasma levels and endocellular retention are lower in adults than in children.[147] Recent experimental evidence however has shown that trimetrexate was succesful in methotrexate-resistant leukemias,[148] and that topotecan, a new topoisomerase I inhibitor, was highly effective in inducing apoptosis and cell death in high-risk radiation-resistant B-lineage ALL.[149] These experimental data certainly require rapid translation into clinical practice. At present, the lack of effective new drugs and the toxicities of reportedly active regimens represent the most serious obstacles to improving retreatment results.

Improved allogeneic and autologous bone marrow transplantation procedures

Second or later CR patients with histocompatible siblings must undergo an early allogeneic BMT. If the patient enters a CR but has no BM family donor, a MUD search is mandatory. This procedure is applicable to younger patients in second CR, without significant complications from prior chemotherapy and not previously (auto)transplanted. Moreover, the MUD search takes time, the chances of finding a donor are slim, and the risk of graft failure or severe graft-versus-host-disease is still relatively high. For these reasons retreatment should go on relentlessly as if there were no MUD, including a final ablative phase supported by autologous bone marrow or ABSC cell rescue.

Because there is some evidence in favor of it and none against it, *in vitro* purging of the autologous marrow graft should be considered. The same issue is totally open as regards ABSC transplantation. The strategy of obtaining highly purified nonleukemic CD34$^+$ stem cells for autotransplants, which has met with partial success in lymphoma patients,[150] may be a valid alternative to or even better than ALL cell-directed purging. There is presently no consensus on whether or how an allogeneic MUD BMT should be carried out at a later stage in autografted patients, but we feel it is highly illogical to leave the certain for the uncertain when time is running out and a further relapse is impending.

Better prophylaxis and treatment of infections, graft rejection and graft-versus-host disease are obviously expected to improve disease-free survival after transplants. However, due to the high risk of BMT failure by recurrence,

efforts must be devoted to improving the conditioning regimen as well. The exact role of total body irradiation (TBI) is being clarified. Both B- and T-lymphoid precursor cells are extremely sensitive to low-dose irradiation,[28,151] which, interestingly, could initiate the apoptosis program[152] or even circumvent pleiotropic drug resistance by causing direct DNA strand breaks. TBI is noncross-resistant with all drugs. For these reasons TBI has long been a mainstay of treatment, although controversy persists about the best dosage and the best way to deliver it. In one study on allogeneic BMT for ALL patients in first CR, single-dose TBI was associated with a lower relapse rate than fractionated irradiation.[153] The efficacy of hyperfractionation was, on the contrary, documented in another study on relapsed ALL of childhood.[154] An increased TBI dosage from 12 to 15.75 Gy was associated with a decreased relapse rate but also with increased nonrelapse mortality in patients with chronic myelogenous leukemia undergoing allogeneic BMT in chronic phase.[155] These deaths were mainly due to interstitial pneumonitis. There is now sufficient experimental evidence to confirm that lymphoid cell survival is abrogated at the 15 Gy level, whereas hyperfractionation could limit pulmonary and gastrointestinal toxicity.[156]

Observations that relapse can follow a 12-Gy TBI dose in radiation resistant B and T-cell ALL subsets are in general agreement with this finding and point to the clinical use of higher TBI dosages.[157,158] With this background, 15-Gy TBI was administered in ten fractions over five days in a pilot study conducted at Mount Sinai Hospital (New York, USA) in a group of leukemia patients, with no untoward acute effects.[156] Hyperfractionated 15-15.75-Gy TBI must be considered in recurrent ALL, particularly in the autologous bone marrow/ABSC setting where the risk of interstitial pneumonitis is lower than in allogeneic transplants, and especially in the presence of radiation-resistant T-cell $CD3^+$ and B-cell $CD24^-$ ALL phenotypes.[157,158] Notably, the radiation dose to the hematopoietic tissue could be increased even further by adopting a combined technique of external TBI plus intravenous ^{131}I-labeled anti-CD45 antibody.[159]

As regards TBI-associated drugs, high-dose teniposide,[160] etoposide[161] and Ara-C[124] were all found to be very effective substitutes for cyclophosphamide. In this last study high-dose Ara-C at 2-3 g/m^2/dose was consistently associated with lower relapse rates than cyclophosphamide, but it was more toxic and caused more nonrelapse deaths. Ara-C at 1-2 g/m^2/dose should be preferred because it is less toxic in adults, though not significantly different in terms of pharmacokinetics and antileukemic power.[162,163] Furthermore, fewer toxicity problems are expected with Ara-C/TBI combinations in autologous transplants. Recently, radiation-free ablative schedules with busulfan-cyclophosphamide[123] and busulfan-etoposide[164] were developed (the latter has not yet been tested in recurrent ALL) and shown to be at least as effective as TBI-containing regimens. These treatments could be reserved for patients failing a prior TBI-based transplant or who received high cumulative radiation dosages to risk sites, but at present it seems unlikely that busulfan could be a worthy substitute for TBI. In a single randomized study conducted in acute leukemia patients, concerning AML patients in first remission undergoing allogeneic BMT, cyclophosphamide-TBI was significantly better than busulfan-cyclophosphamide in terms of leukemia-free survival, survival, relapse rate, regimen-related toxicity and transplant mortality.[165] Moreover, a recent retrospective review of the complete European experience confirmed that survival and disease-free survival of advanced-stage ALL patients undergoing allogeneic or autologous BMT were significantly better with a TBI than with a busulfan regimen.[166]

New developments

Finally, newer research insights must find a definite therapeutic place within the retreatment strategy. Short-term *in vitro* chemosensitivity studies could help select the most appropriate retreatment drugs. Unfortunately, this highly individualized retreatment approach failed in recurrent ALL of children initially treated with BFM protocols,[167] but it has not yet been tested in adults. The use of agents capable of restoring

drug-sensitivity, mainly through induction of apoptosis, should be explored. IL-4 is a strong candidate for such a study in B-precursor ALL,[33] but there may be others to use in diverse ALL subsets.

The new cyclosporin D analogue SDZ PSC 833 was demonstrated to be particularly effective in reverting P-glycoprotein-mediated drug resistance in human leukemic cells.[168,169] Resistance to apoptosis in T-ALL can be circumvented as well;[170] however, short-term and long-term toxicities to both hematological and extra-hematological tissues either induced or facilitated by these agents are virtually unknown in humans, so that these studies will require careful design and supervision. Similarly, the use of IL-2, anti-sense oligonucleotides[171] and α-interferon (in Philadelphia-positive ALL) must undergo further clinical testing. Recently, IL-2 was used to generate killer cells in cultured bone marrow for autologous transplantation.[172]

In summary, evaluation of minimal residual disease, hematopoietic stem cell purging, positive selection of nonleukemic CD34$^+$ cells, reversal of drug resistance, and restoration of altered apoptosis are the most exciting research areas for the 1990s, and deserve to be included in new retreatment protocols for recurrent ALL.

Proposals and guidelines

The management of recurrent ALL in adults remains an extremely difficult task. However, some issues are now in better focus. First, results are generally better with the most intensive reinduction schedules and ablative consolidation treatments, suggesting that *more* is somehow *better*. Thus we must find out exactly whether this is really so, or if it merely results in increased toxicity. This applies especially to ablative treatments for allogeneic/autologous BMT/ABSC transplants, where augmented-dose TBI, drugs alternative to cyclophosphamide, and *in vitro* stem-cell purging procedures should be considered. Second, the mechanisms underlying treatment failure are being elucidated, pushing strongly towards the concurrent exploitation of biologically-oriented strategies. Third, the very short response expected after current salvage therapies makes a time-compressed retreatment plan mandatory; this must be completed before overt progression occurs, i.e. within three months. Delay and uncertainty appear to be highly detrimental and, although many may be reluctant to consider such a tiny space a true remission, we cannot forget that these are the real terms of the question, which go beyond personal opinion and are solely in the interest of the patient.

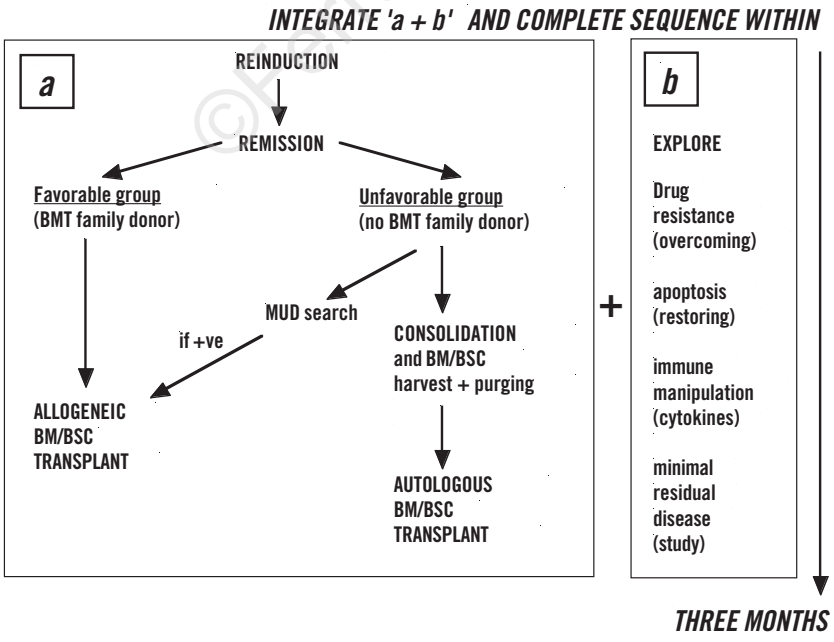

Figure 3. Proposals for the management of recurrent adult ALL.

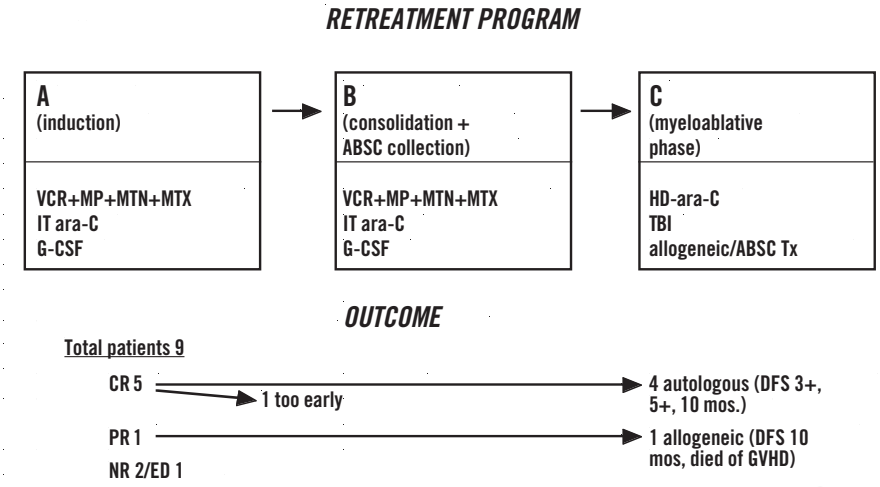

Figure 4. ABC retreatment program. Drugs: VCR, vincristine 2 mg days 1 and 8; MP, methylprednisolone 250 mg/d (course A) and 125 mg/d (course B) days 1-5, 8-12; MTN, mitoxantrone 12 mg/m^2/d (course A) and 6 mg/m^2/d (course B) days 1-3; MTX, methotrexate 1.5 g/m^2 (course A) and 1 g/m^2 (course B) day 8 (folinic acid rescue starting 24 h from end of MTX infusion, 15 mg every 6 hours until MTX plasma level <0.5 μM/l); IT Ara-C, 75 mg intrathecally day 1; G-CSF, granulocyte colony-stimulating factor 5 μg/kg/d from day 10 to neutrophil recovery (course A) and BSC collection (course B); HD-Ara-C, 2 g/m^2 bd days 1-6; TBI, total body irradiation 2 Gy bd days 7-9; Tx, allogeneic/autologous BSC transplant. Definitions: CR, complete remission; PR, partial remission (marrow blast cells reduced by at least 50%); NR, no response (less than PR); ED, early death; DFS, disease-free survival.

Retreatment study proposals emerging from the present survey are summarized in Figure 3.

Some of the concepts discussed in this paper served as a basis for developing the ABC retreatment protocol currently being tested at Bergamo Hospital. The primary objective of this ongoing study was to complete treatment within three months, including a myeloablative phase supported by either allogeneic or autologous BSC graft. Eligible patients were refractory to or relapsing after intensive multi-drug regimens that included intermediate to high cumulative dosages of anthracyclines, cytarabine, podophyllotoxins, cyclophosphamide, and L-asparaginase.[3] Mitoxantrone and high-dose methotrexate were added to vincristine-prednisone because they were active drugs not previously used, whereas the conditioning regimen consisted of high-dose cytarabine at 2 g/m^2/dose plus fractionated 12-Gy TBI. Increasing the TBI dose from 12 Gy to 15 Gy, assessment and reversal of drug resistance, substitution of trimetrexate for methotrexate, restoration of altered apoptosis, and selective positive *purging* of nonleukemic CD34$^+$ BSC for autologous transplant are all possible improvements to consider as the study progresses. Our very preliminary experience (Figure 4) in nine high-risk patients (recurrence = 7, refractory = 2; t(9;22)/BCR$^+$ = 2; T-ALL = 5; age >30 years = 4; prior CR <18 months = 4) documented the feasibility of this approach and warrants its continuation along the guidelines suggested above. These are in no way meant to represent the final answer to a continuing challenge, simply sufficiently clear objectives for both patients and physicians.

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