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editorial

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Randomized clinical trials in adult acute lymphoblastic leukemia: which is the question?

This issue of Haematologica contains the results of a randomized clinical trial conducted by the Spanish Group PETHEMA (see Tables for acronyms), relative to the effects of late intensification therapy in adult acute lymphoblastic leukemia (ALL) [*Ribera et al. Late intensification chemotherapy has not improved the results of intensive chemotherapy in adult acute lymphoblastic leukaemia. Results of a prospective multicenter randomized trial (PETHEMA ALL-89). Haematologica 1998; 83:222-230*]. Mature results from randomized adult ALL trials have not been frequently published in the last years, contrary to the number of unsolved therapeutic questions, so this report is both informative to the readers as well as an indicator of the new editorial policy of the Journal. From my point of view, admittedly that of a non-trialist deeply involved in the management of this illness, it can be profitable to reconsider critically the information gathered from phase III trials and their impact within the scientific community.

The problem of late intensification therapy was previously tackled by the members of the SEG, whose phase III study reached the same conclusions as the PETHEMA Group. Both studies strongly discourage the inception of yet another controlled trial on the same subject, although a criticism may be addressed to the small number of patients assigned to randomization arms (24 and 29 in each arm in the PETHEMA and SEG trial, respectively), to the low-intermediate intensity of the scheduled late intensification regimens, and to the fact that, by definition, patients relapsing early were excluded from both treatment realization and evaluation. So, while the available evidence speaks against late intensification, none can exclude a different result in a larger patient cohort, using an increased-intensity regimen, or in distinct immunobiologic ALL subtypes, particularly in pre-B ALL that shows a consistent tendency to recur until relatively late. The patient number is absolutely crucial. In their most recently published study (Table 2), concerning a different aspect of postremission therapy, the MRC team calculated that the inclusion into the study of 450 patients gave a less than a 65% chance of detecting a 2p=0.05 significance level for the consolidation treatments employed, given the 13% maximal prognostic divergence observed in that study. Nonetheless, clinicians willing to embark on a new study are warned by SEG and PETHEMA study results that late intensification is unlikely to significantly add to the final outcome. They are also warned, from a practical standpoint, that reducing the exposure to anticancer agents improves the patient compliance to the treatment plan and limits the risk of serious late complications. Is this really good news? Essentially, it depends on our expectations. Some will acknowledge the politeness of the randomized trial design and the fact that chemotherapy can be curtailed without apparently affecting outcome, but others will be disappointed by the lack of true therapeutic progress. Actually, in the clinical practice, the consideration giv-

Table 1. Phase III clinical trials in adult ALL: induction phase.

Group	*Question posed*	*Main results*	*Impact*	*Reference: 1st author and source*
CALGB	DNR added to V-P-L-asp	Outcome improved (p=.003)	High	Gottlieb: Blood 1984; 64: 267-74
CALGB	DNR vs Mitox	No difference	Low	Cuttner: Leukemia 1991; 5: 425-31
EORTC	HiDAC added (1 dose)	No difference	Low	Stryckmans: Leukemia 1992; 6 (Suppl 2): 199-203
ECOG	Increased DNR plus AC/TG	Outcome worsened (toxicity)	Low	Cassileth: Leukemia 1992; 6 (Suppl 2):178-81
MRC	DNR vs ID-MTX	No difference (earlier CR with DNR; p=.03)	Low	Durrant: Br J Haematol 1993: 85: 84-92
Mexico city	DOX weekly vs 3-day schedule	No difference	Low	Candelaria: Blood 1993; 82 (Suppl 1): 56a
FGTAALL	DNR vs ZRB	No difference	Low	Fière: J Clin Oncol 1993; 11: 1990-2001
Japan	L-asp added to V-P-DOX	No difference	Low	Nagura: Cancer Chemother Pharmacol 1994;33: 359-65
GIMEMA	CY added to V-P-DNR	No difference	Low	Mandelli: Br J Haematol 1977; 93 (Suppl 2): 144

Abbreviations: CALGB, Cancer and Leukemia Group B; EORTC, European Organization for Research and Treatment of Cancer; ECOG, Eastern Cooperative Oncology Group; MRC, Medical Research Council; FGTAALL, French Group on Therapy for Adult ALL; GIMEMA, Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto; DNR, daunorubicin; V, vincristine; P, prednisone; L-asp, asparaginase; Mitox, mitoxantrone; HiDAC, high-dose ara-C; AC, ara-C; TG, 6-thioguanine; ID-MTX, intermediate-dose methotrexate; DOX, doxorubicin; ZRB, zorubicin; CY, cyclophosphamide.

en to randomized studies is often inferior to their citation index in subsequent papers. This is the matter I wish to comment on in a more detailed manner.

We can turn our attention to published randomized trials and try to understand if and at which extent they influenced the management of ALL patients outside the study setting. Let me first consider the remission induction phase (Table 1). The role of drugs added to the vincristine-prednisone (V-P) backbone combination was evaluated. The landmark CALGB study proved the superiority of a daunorubicin (DNR)-containing regimen over V-P-L-asparaginase alone. Notably, the CALGB DNR schedule was (and still is) 45 mg/m^2 on days 1-3 of treatment. The question of weekly vs a three-consecutive-day schedule for an anthracycline was the matter of a Mexican study, which suggested an advantage for the three-day schedule, but again patient number was too small. In spite of these studies, not all major Groups subsequently adopted or tested further the CALGB-type DNR administrative schedule. Others preferred a weekly DNR delivery,[1] excluded the anthracycline in favor of methotrexate,[2] used doxorubicin instead,[3] doxorubicin by continuous infusion,[4] idarubicin,[5] or high-dose mitoxantrone in combination with high-dose cytarabine.[6] When increasing the DNR dosage from 45 mg/m^2/dose to 80 mg/m^2 was among the study objectives, the response rate declined from 70% to 56% due to increased toxicity. However, the response rate was 91% in a recent uncontrolled study with DNR 60 mg/m^2/d on days 1-3,[7] and the results were still good when the DNR dosage was reduced to 25 mg/m^2/d.[8] Thus, apart from an almost general consensus on the usefulness of an anthracycline, there is no specific agreement on drug type and schedule. Because the remission rate was 80% or greater in the majority of the trials cited and confirming a significant difference, if any, would require the randomization of thousands of patients, there may be no further demand of controlled studies on this subject. As regards to L-asparaginase, the single randomized study from Japan reported no statistically significant prognostic difference between patients who received or did not receive this drug. Notwithstanding it, most Groups with relevant exceptions (*MD Anderson Cancer Center, Memorial Sloan-Kettering Cancer Center*) still adopt this drug front-line, though at heterogeneous dose ranges. Its therapeutic contribution remains unclear. Lastly, another drug, cyclophosphamide or single-shot high-dose cytarabine, were added to three or four drug combinations. The results from the GIMEMA randomized study argued against the addition of cyclophosphamide to V-P plus DNR. At variance, both CALGB and MD Anderson Groups obtained their best hitherto remission results after including this drug into their respective induction protocols.[9,10] The randomized EORTC study on high-dose cytarabine was of little interest, being that no significant activity is expected from this drug after a single administration.

The situation about post-remission consolidation phase is similar. As in PETHEMA and SEG studies, assessing the role of late intensification, the majority of trials confirmed an equivalence rather than demonstrating the superiority of one treatment over another (Table 2). In this way, the therapeutic strategy was not implemented and the study impact was marginal or nil. An exception may occur with study 04/89 from the GMALL Group, reporting significantly improved results from intensification therapy with both mitoxantrone/high-dose cytarabine and L-asparaginase/high-dose methotrexate, as compared with prior protocols 01-03. However, there was no significant difference between study arms and the evaluation of efficacy was once again based on a retrospective analysis. The MRC concluded that, to obtain a final answer on the question of consolidation intensity, a much greater patient accrual would be necessary, given an expected disease-free survival increment slightly above 10%. It was probably this figure rather than the patient number that convinced the Group members to test a totally different argu-

Table 2. Phase III clinical trials in adult ALL: post-remission consolidation phase.

Group	*Question posed*	*Main results*	*Impact*	*Reference: 1st Author and source*
GIMEMA	Extended consolidation	No difference	Low	Mandelli: Br J Haematol 1989; 71:377-86
CALGB	DNR plus AC added	No difference	Low	Ellison: J Clin Oncol 1991; 9:2002-15
EORTC	1 mo. vs 4 mos.	No difference	Low	Stryckmans: Leukemia 1992; 6(Suppl 2):199-203
SWOG	L1OM vs DAT/MTX/L-asp	No difference	Low	Petersdorf: Blood 1993; 82(Suppl 1):193a
GMALL	Mitox/HiDAC vs HD-MTX/L-asp	No difference (improved over prior regimens)	Too early	Hoelzer: Blood 1993; 82(Suppl 1): 193a
SEG	Late intensification	No difference	Low	Omura: Leuk lymphoma 1994; 15:71-8
GIMEMA	Consolidation vs maintenance	No difference	Low	Mandelli: Br J Haematol 1977; 93(Suppl 2):144
MRC	Consolidation intensity	No difference (improved with early block)	Uncertain	Durrant: Br J Haematology 1997; 99:84-92
PETHEMA	Late intensification	No difference	Low	Ribera: Haematologica 1998; 83:222-230

Abbreviations (see Table 1): SWOG, Southwestern Oncology Group; GMALL, German Multicenter ALL; SEG, Southeastern Oncology Group; PETHEMA, Program for the Study and Treatment of Malignant Hemopathies; DAT, daunorubicin/ara-C/6-thioguanine; HD, high-dose.

ment in their subsequent trial, that is autologous vs allogeneic bone marrow transplant.

The randomized studies on allogeneic bone marrow transplant (Table 3) versus other post-remission strategies suffered from the same numerical limitations, but the difficulty to judge is even worse for those who believe that this ultimate procedure should not be indiscriminately applied to all cases with a suitable donor, regardless the risk class. This means that, on a purely quantitative basis, there may well be no further possibility of performing a randomized trial on allogeneic bone marrow transplant in first remission adult ALL, least to include good-risk patients with a ≥ 50% likelihood of prolonged disease-free survival with chemotherapy alone. If only high-risk patients are included, an appropriate choice in the most recent PETHEMA study, the randomization of too few patients (52 total cases assigned to three different treatment arms over 45 months in the PETHEMA trial) will eventually hamper the evaluation and interpretation of results.

These considerations explain why new pilot, uncontrolled studies are being regularly initiated elsewhere (*MD Anderson Cancer Center, Bay Group, Memorial Sloan-Kettering Cancer Center, GMALL Group, Verona University Hospital, Bergamo Hospital* collaborative trials). They document the impending crisis of randomized clinical trials in adult ALL, as traditionally intended, which in my opinion stems partly from the kind of questions so far addressed and partly from the increased quality of nonrandomized trials. For instance, there is quite sound evidence from uncontrolled trials that B/L3-ALL benefits greatly from a specific therapeutic approach[11,12] and that, similarly, T-cell ALL benefits from GMALL/CALGB-type intensive consolidation schedules. There is no such evidence from any of the controlled studies available. As a result, several Centers worldwide are adopting the former risk-specific, *uncontrolled* but highly active schedules and disregard the information from randomized trials. The fact that this information is different means little when it is not better.

The examples of B/L3-ALL and T-cell ALL bring us directly to the key question, the management of discrete ALL and risk subsets with selected drugs, dosages and combinations. Known ALL subsets vary greatly in their chemosensitivity pattern, as documented by *in vitro* studies and some retrospective clinical reports. The pharmacologic basis of total therapy programs for childhood ALL was recently reviewed,[13] as well as the role of anthracyclines and high-dose methotrexate.[14-16] These and other reports underscore the tight connection between certain drugs and the improved clinical outcome of discrete ALL subsets. This seems to occur with the antimetabolites in hyperdiploid B-precursor ALL; with high-dose methotrexate in children rather than adult ALL; and with anthracyclines in $CD10^+$ B-precursor ALL. Complementary evidence showed drug resistance mechanisms to be among the primary factors responsible for treatment and retreatment resistance.[13,17,18] T cell ALL is commonly said to be extremely sensitive to cyclophosphamide, high-dose cytarabine, and perhaps podophyllotoxins. This was never formally tested and not all the clinical studies employing one or more of these agents reported significantly improved results. There may be room for innovative studies in this field as well as in that of Philadelphia chromosome-positive ALL and, in general, in the whole field of drug resistance and the newer biological therapies.

Clearly, much remains to be done but time has probably come, for randomized trials, to target major therapeutic questions raised by high quality phase II studies, supported by preclinical research data and related to distinct disease entities and risk profiles. No one doubts that only randomized trials can properly deal with these questions. Let's ask the good ones.

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Table 3. Phase III clinical trials in adult ALL: allogeneic BMT versus other treatment modalities.

Group	*Question posed*	*Main results*	*Impact*	*Reference: 1st author and source*
EORTC	AlloBMT vs chemotherapy/ABMT*	Trend favouring AlloBMT (p<.1)	Low	Stryckmans: Leukemia 1992; 6(Suppl 2):199-203
PV-TO-GE	AlloBMT vs chemotherapy/ABMT*	No difference	Intermediate	Bernasconi: Leukemia 1992; 6 (Suppl 2):204-8
FGTAALL	AlloBMT vs chemotherapy/ABMT*	No difference	Low	Fière: J Clin Oncol 1993; 11:1990-2001
BGMT	AlloBMT vs ABMT*	Outcome improved by AlloBMT (p<.001)	Intermediate	Attal: Blood 1995; 86:1619-28
	IL-2 post ABMT	No difference	Low	
City of Hope	AlloBMT vs chemotherapy*	No difference	Too early	Forman: Blood 1995; 86(Suppl 1):616a
PETHEMA	AlloBMT vs chemotherapy/ABMT*	No difference	Low/too early	Ribera: Ann Hematol 1997; 74(Suppl 1):163a

**Assignement to allo-BMT by HLA identity .*
Abbreviations (see Tables 1-2): allo-BMT, allogeneic bone marrow transplant; ABMT, autologous bone marrow transplant; PV-TO-GE, Pavia-Turin-Genoa; BGMT, Bordeaux, Grenoble, Marseille, Tolouse; IL-2, interleukin-2.

References

1. Hoelzer D, Thiel E, Ludwig WD, et al. Follow-up of the first two successive German multicenter trials for adult ALL (01/81 and 02/84). Leukemia 1993; 7(Suppl 2):S130-4.
2. Wiernik PH, Dutcher JP, Paietta E, et al. Long-term follow-up of treatment and potential cure of adult acute lymphocytic leukemia with MOAD: a non-anthracycline containing regimen. Leukemia 1993; 7:1236-41.
3. Bassan R, Battista R, Rohatiner AZS, et al. Treatment of adult acute lymphoblastic leukemia (ALL) over a 16 year period. Leukemia 1992; 6(Suppl 2):186-90.
4. Kantarjian HM, Walters RS, Keating MJ, et al. Results of the vincristine, doxorubicin, and dexamethasone regimen in adults with standard- and high-risk acute lymphocytic leukemia. J Clin Oncol 1990; 8:994-1004.
5. Bassan R, Battista R, Corneo G, et al. Idarubicin in the initial treatment of adults with acute lymphoblastic leukemia: the effect of drug schedule on outcome. Leuk Lymphoma 1993; 11:105-10.
6. Weiss W, Maslak P, Feldman E, et al. Cytarabine with high-dose mitoxantrone induces rapid complete remissions in adult acute lymphoblastic leukemia without the use of vincristine and prednisone. J Clin Oncol 1996; 8:994-1004.
7. Linker CA. Risk-adapted treatment of adult acute lymphoblastic leukemia (ALL). Leukemia 1997; 11(Suppl 4):S24-7.
8. Todeschini G, Meneghini V, Pizzolo G, et al. Relationship between daunorubicin dosage delivered during induction therapy and outcome in adult acute lymphoblastic leukemia. Leukemia 1994; 8:376-81.
9. Larson RA, Dodge RK, Burns CP. A five-drug remission induction regimen with intensive consolidation for adults with acute lymphoblastic leukemia: Cancer and Leukemia Group B study 8811. Blood 1995; 85:2025-37.
10. Kantarjian H. Remaining challenges in adult acute lymphocytic leukaemia. Trends in Onco-Hematology 1996; 4:79-81.
11. Hoelzer D, Ludwig W-D, Thiel E, et al. Improved outcome in adult B-cell acute lymphoblastic leukemia. Blood 1996; 87:495-508.
12. Lerede T, Bassan R, Rossi A, et al. Therapeutic impact of adult-type acute lymphoblastic leukemia regimens in B-cell/L3 acute leukemia and advanced-stage Burkitt's lymphoma. Haematologica 1996; 81:442-9.
13. Pui C-H, Relling MV, Masson E, Rivera GK, Crist WM, Evans WE. Pharmacokinetic resistance in childhood leukemia. In: Pieters R, Kaspers GJL, Veerman AJP, eds. Drug resistance in leukemia and lymphoma. II. Amsterdam: Harwood Academic Publishers; 1997. p. 1-7.
14. Bassan R, Lerede T, Rambaldi A, Buelli M, Viero P, Barbui T. The use of anthracyclines in adult acute lymphoblastic leukemia. Haematologica 1995; 80:280-91.
15. Goker E, Tin JL, Trippett T et al. Decreased polyglutamylation of methotrexate in acute lymphoblastic leukemia blasts in adults compared to children with this disease. Leukemia 1993; 7:1000-4.
16. Kaspers GJL, Smets LA, Pieters R, van Zantwijk CH, van Wering ER, Veerman AJP. Favorable prognosis of hyperdiploid common acute lymphoblastic leukemia may be explained by sensitivity to antimetabolites and other drugs: results of an *in vitro* study; Blood 1995; 85: 751-6.
17. Testi AM, Moleti ML, Giona F, et al. A single high dose of idarubicin combined with high-dose ABA-C (MSKCC ALL-3 protocol) in adult and pediatric patients with acute lymphoblastic leukemia. Experience at the University La Sapienza of Rome. Haematologica 1997; 82:19-22.
18. Bassan R, Lerede T, Barbui T. Strategies for the treatment of recurrent acute lymphoblastic leukemia in adults. Haematologica 1996; 81:20-36.