without isolation and identification of the causative agent [1]. This is particularly important in light of the poor intrinsic activity of the cephalosporins and of the lack of intracerebral penetration of the aminoglycosides, a combination that is currently used as empirical treatment of fever and suspected infection in neutropenic cancer patients. Optimal treatment of listerial infections remains controversial. A combination of ampicillin and gentamicin is generally recommended, but other options are possible, including cotrimoxazole, rifampin and vancomycin [4].

In conclusion, the occurrence of brain abscesses due to *L. monocytogenes* in this 6-year-old girl should alert pediatricians against this entity. Despite the severity of the clinical course, this infection was treated successfully without any neurological sequela and did not preclude the continuation of the antineoplastic treatment, including allogeneic bone marrow transplantation.

1. Dee RR, Lorber B. Brain abscess due to *Listeria monocytogenes*: case report and literature review. *Rev Infect Dis* 1986, **8**, 968–977.
2. Pollock SS, Pollock TM, Harrison MJG. Infection of the central nervous system by *Listeria monocytogenes*: a review of 54 adult and juvenile cases. *Q J Med* 1984, **53**, 331–340.
3. Dykes A, Baraff LJ, Herzog P. *Listeria* abscess in an immunocompromised child. *J Pediatr* 1979, **94**, 72–74.
4. Gellin BG, Broome CV. Listeriosis. *JAMA* 1989, **261**, 1313–1320.
5. Fleming DW, Cochio SL, MacDonald KL, *et al.* Pasteurized milk as a vehicle of infection in an outbreak of lister. *N Engl J Med* 1985, **312**, 404–407.
6. Linnan MJ, Mascola L, Xiao DL, *et al.* Epidemic listeriosis associated with Mexican-style cheese. *N Engl J Med* 1988, **319**, 823–828.
7. Schlech WF, Lavigne PM, Bortolusse R, *et al.* Epidemic listeriosis: evidence for transmission by food. *N Engl J Med* 1983, **308**, 203–206.
8. Hantel A, Dick JD, Karp JE. Listeriosis in the setting of malignant disease. Changing issues in an unusual infection. *Cancer* 1989, **64**, 516–520.
9. Khardori N, Berkey P, Hayat S, Rosenbaum B, Bodey GP. Spectrum and outcome of microbiologically documented *Listeria monocytogenes* infections in cancer patients. *Cancer* 1989, **64**, 1968–1970.
10. Viscoli C, Van der Auwera P, Meunier F. Gram-positive infections in granulocytopenic patients: an important issue? *J Antimicrob Chemother* 1989, **21**, 149–156.
11. Armstrong D, Polsky B. Central nervous system infections in the compromised host. In: Rubin LH, Young LS. *Clinical Approach to Infections in the Compromised Host*, 2nd ed. New York, Plenum Medical, 1988, 165–191.
12. Oren-Harris J, Marquez J, Swerdloff MA, Magana IA. *Listeria* brain abscess in the acquired immunodeficiency syndrome. *Arch Neurol* 1989, **46**, 250.
13. Ochs J, Mulhern RK. Late effects of antileukemic treatment. *Pediat Clin North Am* 1988, **35**, 815–834.

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Postremission Chemotherapy in Adult Acute Non-lymphoblastic Leukaemia Including Intensive or Non-intensive Consolidation Therapy

Monica Giordano, Alberto Riccardi, Margherita Girino, Silvia Brugnatelli, Paolo Scivetti, Renata Luoni, Rosangela Invernizzi and Edoardo Ascari

From October 1983 to December 1988, 84 consecutive adult patients with acute non-lymphoblastic leukaemia (ANLL; median age = 51 yr) were uniformly treated to induce remission (CR) with intravenous vincristine and cytarabine sequentially followed by daunomycin and infusion cytarabine. From October 1983 to December 1985 consolidation was non-intensive (2 courses with the same drugs used for induction) (protocol ANLL83: 27 patients, median age = 45). From January 1986 to December 1988 consolidation was intensive (4 courses of vincristine and cytarabine sequentially followed by etoposide plus thioguanine or amsacrine) (protocol ANLL86: 57 patients, median age = 57). Excluding early deaths, the CR rate was 71.6%. Median CR, responsive patient survival and overall survival were 11.1, 15.3 and 8.5 mo, respectively. For protocol ANLL83 and ANLL86, median CR was 8.7 and 13.2 mo ($P < 0.05$) and median survival was 13.1 and 16.9 mo ($P < 0.05$) for responders and 8.0 and 9.2 mo (P not significant) for all patients. Intensive consolidation including drugs not previously used for induction seems to prolong CR duration and responder survival in adult ANLL.
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INTRODUCTION

A WAY OF administering postinduction therapy to adult acute non-lymphoblastic leukaemia (ANLL) patients after remission (CR) is consolidation therapy, where short intensive cyclic therapy is given for 3–6 months and may be followed or not by maintenance [1]. For consolidation, options can be made for both the choice of drugs administered (only those employed for induction can be used or new cytostatics may be added) and their dosage [1]. The prerequisites which define a consolidation course as being intensive or non-intensive are not clear-cut but, as a guideline, an intensive course should produce, in a CR patient, heavy cytopenia, i.e white blood cell (WBC) count of less than 1.0×10^9/l and a platelet count of less than 50×10^9/l about 2 weeks following its completion [2].

In this paper we report data on a treatment program for ANLL which was started in 1983 [3]. Induction treatment was the same for all patients. In the first group of CR patients, consolidation was non-intensive and employed the same drugs used for induction. In patients treated subsequently, consolidation was intensive and employed cytostatics that were not used for induction. Intensive consolidation apparently resulted in increased CR and responder survival duration.

MATERIALS AND METHODS

Patients

84 consecutive untreated ANLL patients entered this prospective, non-randomised study between October 1983 and December 1988 (Table 1). No patient with a diagnosis of AL was excluded due to advanced age or history of preleukaemia (8 patients). Median age was 51 (range 16–78) and the male:female ratio was 45:39. Distribution of FAB subtypes was as follows: M1: 12 patients; M2: 14; M3: 14; M4: 30; M5: 10; M6:2; and M7:2. Chromosomal abnormalities were found in 10 patients [translocation 8/21, 2 cases; trisomy 8, 3 cases; monosomy 7, 2 cases; trisomy 11, 1 case; inv 16 (p13 q22), 1 case; and 1q+, 1 case].

Cytostatic treatment

Induction therapy. For all patients, two courses of induction treatment were planned at a 14–21 day interval. The induction course was derived from previous *in vivo* data, indicating that the intravenous push administration of vincristine and of moderate dose cytarabine increased the tritiated thymidine labelling index in most patients with AL, i.e. synchronised blasts in S phase [4, 5], and this, in turn, increased the effectiveness of a sequentially administered anthracycline in reducing the peripheral blood blasts [4].

In each course, patients initially received vincristine (2 mg intravenously on day 1) and cytarabine (75 mg/m^2/12 h directly intravenously from day 1 to 4). Daunomycin (80 mg/m^2 intravenously) was then given on days 5 and 7, and cytarabine (200 mg/m^2/day by continous infusion) on days 6 and 7. A bone marrow (BM) aspirate and/or biopsy was performed 10–14 days after each course. Complete remission was defined as disappearance of BM blasts with normal haematological values (granulocytes $> 1.5 \times 10^9$/l, platelets $> 100 \times 10^9$/l and haemoglobin $>$ 11g/dl) maintained for at least 1 month without transfusions. Partial remission was not used as a criterion for defining response.

Consolidation therapy

The CR patients recruited between November 1983 and December 1985 (protocol ANLL83) received non-intensive consolidation with 2 courses of the same drugs and with the same drug sequencing used for induction (but with only one dose of both daunomycin and infusion cytarabine, on day 5).

The CR patients recruited between January 1986 and December 1988 (protocol ANLL86) received intensive consolidation using 4 courses, including cytostatics not used for induction. In each consolidation course, these new drugs were given sequentially to vincristine and cytarabine, as in the induction course. In practice, vincristine and cytarabine were scheduled as in the induction course, and followed by etoposide (100 mg/m^2/day by 2 h intravenous infusion) plus thioguanine (100 mg/m^2/day orally) for 5 days (1st and 3rd course) or by amsacrine (60 mg/m^2 by 2 h intravenous infusion) on day 5 (2nd and 4th course).

Post-consolidation treatment

After consolidation, patients of protocol ANLL83 were given a 1.5-year maintenance regimen in which different cytostatics were given every 4–6 weeks in order of circumventing drug resistance in residual leukaemia [6, 7]. The following drugs and drug combinations were used: TRAP (courses 1, 6 and 11) [6], VP 16 213 (150 mg/m^2/day intravenously, days 1 to 5, courses 2, 7 and 12), POMP (course 3) [6], cytarabine plus thioguanine (cytarabine 100 mg/m^2/12 h intravenous plus 6-TG, 100 mg/m^2/day orally, days 1–5, courses 4, 9 and 14), COAP (courses 5, 10 and 15) [6], Iomustine (80 mg/m^2 orally, day 1, course 8) and cyclophosphamide (1 g/m^2/day by 2 h intravenous infusions, days 1 and 2, course 13).

The CR patients of protocol ANLL86 were randomised to receive or not receive the above maintenance program.

Supportive measures

These measures did not change throughout the whole study period and have been reported in a previous paper [3].

Result analysis

Remission duration is calculated from the data of CR to the data of relapse. Survival is calculated from the start of therapy. Survival and remission curves were constructed according to the method of Berkson and Gage [8] and analysed with the Lee–Desu procedure [9].

RESULTS

No patient in our series had bone marrow transplantation. The results obtained are summarised in Tables 1 and 2 and Figs 1 and 2.

CR rate

Table 2 furnishes the CR rates according to the categories of patients included in the evaluation. Excluding patients who died (due to consequences of cytopenia, i.e haemorrhage and/or infection) before starting chemotherapy or before completing induction, 48/67 (71.6%) patients achieved CR. Of 19 patients

Table 1. Main clinical characteristics of the studied population

Protocol	ANLL83 + ANLL86	ANLL83	ANLL86	*P*
No. of patients	84	27	57	—
M/F	45/39	15/12	30/27	NS
Median age, yr (range)	51 (16–78)	45 (16–77)	57 (20–78)	NS
FAB subtypes				
$M_1/M_2/M_3$	12/14/14	4/4/6	8/10/8	NS
$M_4/M_5/M_6/M_7$	30/10/2/2	8/4/0/1	22/6/2/1	

All patients were treated to induce remission (CR) with sequential vincristine, arabinosylcytosine and daunomycin. Patients on protocol ANLL83 and ANLL86 received non-intensive and intensive consolidation therapy, respectively.

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Table 2. Remission rates according with exclusion criteria

Protocol	ANLL83 + ANLL86 No. CR	%	ANLL83 No. CR	%	ANLL86 No. CR	%
All entered patients	48/84	57.1	15/27	55.5	33/57	57.8
With exclusion						
A	48/78	61.5	15/24	62.5	33/54	61.1
A + B	48/67	71.6	15/20	75.0	33/47	70.2
A + B + C	48/59	81.3	15/16	93.7	33/43	76.7
CR following 1st course	36/48	74.6	11/15	73.0	25/33	76.0

A = not treated (6 patients = 7.1%); B = early deaths (11 patients = 13.0%); C = previous myelodysplasia and/or treatment (8 patients = 9.5%).

who failed to achieve CR, 2 died from haemorrhage and/or infection during BM aplasia and 17 had resistant disease. There were no differences in CR rate between protocols ANLL83 and ANLL86 and the 75% of responsive patients achieved CR following the first course.

Among patients who completed induction, patients aged less than the median age (43 and 54 yr for protocols ANLL83 and ANLL86, respectively) had CR rates greater than older patients (for protocol ANLL83, 60 and 90%, respectively, and for protocol ANLL86 58.3 and 82.6%). No difference in CR duration was seen depending on responsive patient age.

CR duration

Median CR was 11.1 months for all patients. It was 8.7 months for the 15 CR patients of protocol ANLL83 (who received non-intensive consolidation with the same drugs used for induction) and 13.2 for the 33 patients of protocol ANLL86 (who received intensive consolidation with cytostatics other than those used for induction) ($P < 0.05$) (Fig. 1). 7/15 CR patients on protocol ANLL83 and 18/33 CR patients on protocol ANLL86 relapsed before completing consolidation. No difference in CR duration has been seen so far for the remaining 15 protocol ANLL86 patients depending whether they received (7 patients) or did not receive (8 patients) maintenance.

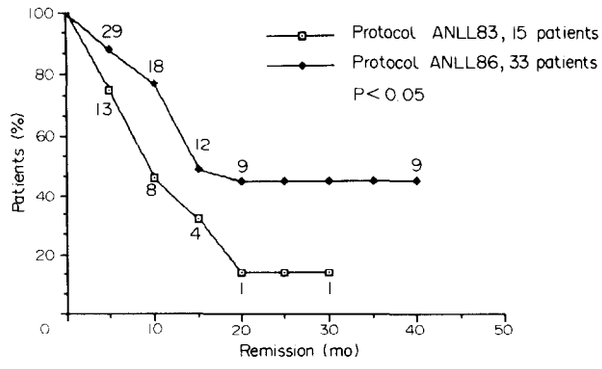

Fig. 1. Remission duration according with consolidation therapy, that was non-intensive in protocol ANLL83 and intensive in protocol ANLL86 (numbers indicate patients at risk).

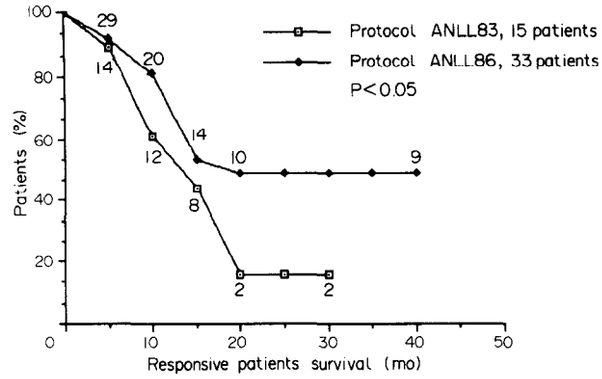

Fig. 2. Duration of responsive patient survival according with consolidation therapy (numbers indicate patients at risk).

Survival

56/67 patients who completed induction (18/20 of protocol ANLL83 and 38/47 of protocol ANLL86) have died. Median survival was 8.5 months for all patients who had been treated (including early deaths) and 15.3 months for those who had responded to therapy. No difference in overall survival is seen between protocol ANLL83 and ANLL86. Responsive patients of protocol ANLL86 had a longer median survival (16.9 months) than those of protocol ANLL83 (13.1 months) ($P < 0.05$) (Fig. 2).

Toxicity

Fever >38°C following the first course was present in 48/67 cases who completed induction. The nadir of WBC (0.4×10^9/l) was reached on day 10 following the end of treatment (WBC were $< 0.5 \times 10^9$/l for a median time of 13 days), and the nadir of platelets (20×10^9/l) was reached on day 14 following the end of treatment (platelets were $< 50 \times 10^9$/l for a median time of 16 days). Both fever and haematological toxicity were less severe during the second course.

As expected, toxicity during consolidation was mild for protocol ANLL83 and quite severe for protocol ANLL86. In protocol ANLL83, only an occasional consolidation course gave granulocyte counts $< 1.0 \times 10^9$/l and/or platelet counts $< 50 \times 10^9$/l, while in protocol ANLL86 (where 4 courses of more aggressive therapy were administered) 68% of CR patients had these low values at least one time during consolidation (the cytopenia phase lasted a median time of 5 days); 48% had them twice and the 21% for three or four times. Accordingly, both fever and requirements for supportive therapy were much more frequent in protocol ANLL86 than ANLL83. However, no patient died due to complications related to consolidation-induced cytopenia.

DISCUSSION

The presented data suggest that intensive consolidation following CR results in increased CR and responder survival duration of ANLL adult patients.

Induction results indicate that the induction schedule we used was well tolerated and effective in inducing CR. Excluding patients who died before or while in induction due to cytopenia (more probably related to leukaemia than to treatment-induced aplasia) (Table 2) [10], the 13.0% early deaths is acceptable during induction for adult AL. The 71.6% CR rate among patients who completed induction compares well with the CR rates obtained in recent investigations [1]. This is especially true if we consider that the median age is higher in our study (51 yr)

than in most reported series, and that median age is a parameter with a strong influence on the CR rate [1].

Sequencing vincristine, cytarabine and daunomycin for induction was based on previous *in vivo* cytokinetic data, indicating that cytostatics have increased effectiveness when administered at the time of S-phase synchronisation induced by vincristine and medium dose cytarabine [4], an effect similar to that reported in *in vitro* experiments using colony stimulating factors (CSFs) before chemotherapy [11]. The good effectiveness of this drug schedule in this quite large series supports that cytokinetic based protocols are useful for inducing CR in AL, although this issue is still unresolved. In fact, some investigations have reported CR advantages in administering cytostatics at time of S-phase blast synchronisation or recruitment [12–17] but this is not confirmed in other studies [18–19] and a definite confirmation through randomised studies is lacking.

For the first 15 responsive patients consolidation was non-intensive and used only the same drugs (vincristine, cytarabine and daunomycin) already employed for induction. In the 33 patients who responded subsequently, consolidation was intensive and contained also cytostatics (etoposide; thioguanine and amsacrine) that were not previously employed. Although this was not a randomised study, intensive consolidation resulted in increased CR and responder survival duration (both induction treatment and supportive measures were the same throughout the whole study).

There is no consensus in the literature on the best post-remission policy [1, 20]. Our data are in keeping with those from two large randomised studies, in which increasing the amount of therapy given for both induction and consolidation [21] or using for consolidation cytostatics other (high dose cytarabine and/or amsacrine and/or 5-azacytidine) than those (cytarabine and daunomycin) employed for induction [22] have prolonged CR and survival duration. However, there are reports contrasting these data, that were reviewed in detail elsewhere [1]. As an example, the advantages of using new drugs for consolidation (including high-dose cytarabine) [23, 24] has been questioned and those of greatly increasing the drug dosage (with BM transplantation rescue) are still not demonstrated [25]. Another example is that administering consolidation before maintenance with the same drugs (cytarabine plus daunomycin plus thioguanine) used for induction is not superior to maintenance alone [26].

These widely contrasting personal and literature data hamper the belief that an empirically devised postinduction chemotherapy in ANLL is crucial in improving the final prognosis of this disease, i.e. patient survival. Obtaining a better quality CR is probably more advantageous. Since no other conventional cytostatic regimen is more effective than cytarabine and anthracyclines in inducing CR, there are two possible ways for lowering residual disease at CR. First, using granulocyte (and/or granulocyte–macrophage) CSFs as normal haemopoietic cell rescue can allow to increase the doses of cytarabine and anthracyclines given for induction [27, 28]. A prerequisite for this approach is that it must be definitely proved that culture studies on individual patient cells [11, 29, 30] can definitely exclude that these stimulating factors also increase blast regeneration. Second, the best way of administering cell cycle-specific or aspecific drugs to lower residual leukaemia could be based on knowing the relative aliquots of in- and out-of-cycle blasts. Exploiting pretreatment kinetic differences in the individual ANLL patient can now be done using the *in vivo* bromodeoxyuridine [31] and flow cytometry and the Ki-67 monoclonal antibody [32, 33] techniques.

1. Riccardi A, Giordano M, Girino M. Treatment of adult acute non lymphoblastic leukemia: a computer aided analysis. *Haematologica* 1987, **72**, 71–78.
2. Zittoun A (for the EORTC Leukemia–Lymphoma group). High dose cytosine arabinoside plus AMSA for reinduction or consolidation maintenance in acute myelogenous leukemia. In: Hagenbeek A, Lowenberg B. eds. *Minimal Residual Disease in Leukemia*. Dordrecht, Martinus Nijhoff, 1986, 159–166.
3. Riccardi A, Invernizzi R, Girino M, *et al.* Sequential vincristine, arabinosylcytosine and daunomycin induction therapy in adult acute leukemia. *Haematologica* 1986, **71**, 129–133.
4. Riccardi A, Mazzini G, Montecucco CM, *et al.* Sequential vincristine, arabinosylcitosine and adriamycin in acute leukemia: cytologic and cytokinetic studies. *Cytometry* 1982, **3**, 104–109.
5. Montecucco CM, Riccardi A, Cresci R, Mazzini G, Ascari E. Cytokinetic changes in the peripheral blood of leukemic patients during cytostatic therapy. Effect of arabinosylcytosine. *Bas Appl Histochem* 1980, **24**, 423–434.
6. Spiers ASD. Chemotherapy of acute leukemia. *Clin Hematol* 1972, **1**, 144–155.
7. Buchner T, Urbanitz D, Hiddemann W, *et al.* Intensified induction and consolidation with or without chemotherapy for acute myeloid leukemia (AML): two multicenter studies of the German AML Cooperative Group. *J Clin Oncol* 1985, **2**, 1583–1589.
8. Berkson J, Gage RP. Calculation of survival rates for cancer. *Proc Staff Meeting Mayo Clin* 1950, **25**, 270–280.
9. Lee TE, Desu MM. A computer program for comparing K samples with right-censored data. *Comput Programs Biomed* 1972, **2**, 315–322.
10. The Toronto Leukemia Study Group. Results of chemotherapy for unselected patients with acute myeloblastic leukemia: effect of exclusion on interpretation of results. *Lancet* 1986, 786–788.
11. Giordano M, Pedrazzoli P, Danova M, *et al.* Modulation of leukemic cell proliferation by haemopoietic growth factors and cytosine arabinoside (Ara-c) (abstr.). XIV International Conference on Analytical Cytology 1990, 108.
12. Vaughan WP, Karp JE, Burke PJ. Long chemotherapy free remission after single cycle timed sequential chemotherapy for acute myelocytic leukemia. *Cancer* 1980, **45**, 859–865.
13. Dahl GV, Kalwinsky DK, Murphy S, *et al.* Cytokinetically based induction chemotherapy and splenectomy for childhood acute non lymphocytic leukemia. *Blood* 1982, **60**, 856–863.
14. Saponara BS, Rothemberg SP, Villamena D. Cytarabine and thioguanine for acute non lymphocytic leukemia. A new look. *Arch Intern Med* 1984, **139**, 1277–1290.
15. Büchner T, Kamanbroo D, Urbaniz D, Hiddenman W, van de Loo J. Induktionsbehandlung der akuten myeloischen leukamie mit cytosin arabinosid daunorubicin, zusazlicher effekt von ifosfamid und vincristin. *Blut* 1978, **36**, 371–376.
16. Kremer WB, Vogler WR, Chang YK. An attempt at synchronization of marrow cells in acute leukemia. *Cancer* 1976, **37**, 390–403.
17. Lampkin BC, McWilliams NB, Mauer AM, Flessa HC, Hake DA, Fisher V. Manipulation of the mitotic cycle in the treatment of acute myelogenous leukemia. *Br J Haematol* 1976, **32**, 29–40.
18. MacKinney AA, Flynn B. Cytosine arabinoside modulation of the mitotic cycle in the treatment of adult acute leukemia. *Am J Haematol* 1979, **5**, 93–99.
19. Sutow VW, Thomas D, Stauber CP, *et al.* Study of cytosine arabinoside (NSC-63878) plus vincristine (NSC-67574) prednisone (NSC-1023) and L-asparaginase (NSC-109229) for remission induction in advanced acute leukemia in children. *Cancer Treat Rep* 1976, **60**, 591–594.
20. Lichman MA, Henderson ES. Acute mylogenous leukemia. In: Williams WJ, Bentler E, Ersler AJ, Lichman MA eds. *Hematology* New York, McGraw-Hill, 1990, 251–272.
21. Bell R, Rohatiner AZS, Slevin ML, *et al.* Short-term treatment for acute myelogenous leukemia. *Br Med J (Clin Res)* 1982, **284**, 1221–1224.
22. Winton EF, Vogler WR, Raney M. A randomized trial of postinduction therapy for acute myeloblastic leukemia (AML) (abstr.). *Blood* 1985, **66**, (Suppl. 1), 212a.
23. Weiner RS, Raney M, Elfenbein GJ, *et al.* Treatment of residual

disease in AML: interim of analysis of a Southeastern Cancer Study Group prospective randomized clinical trial. In: Hagenbeek A, Lowenberg B. eds. *Minimal Residual Disease in Leukemia*. Dordrecht, Martinus Nijhoff, 1986, 167–179.
24. Zittoun R (for the EORTC Leukemia-Lymphoma Group). High dose cytosine arabinoside plus Amsa for reinduction or consolidation maintenance in acute myelogenous leukemia. In: Hagenbeek A, Lowenberg B, eds. *Minimal Residual Disease in Leukemia*. Dordrecht, Martinus Nijhoff, 1986, 159–166.
25. Mayer RJ. Chemotherapy versus allogenic bone marrow transplantation (ABMT) in first remission acute myeloblastic leukemia (abstr.). Third International symposium on minimal residual disease in acute leukemia, Rotterdam, 1990, 28.
26. Cassileth PA, Begg CB, Bennet JM, *et al.* A randomized study of the efficacy of consolidation therapy in adult acute non lymphocytic leukemia. *Blood* 1984, **63**, 843–847.
27. Büchner W, Hiddemann M, Koeningsmann M, *et al.* Human recombinant granulocyte macrophage colony stimulating factor (GM-CSF) for acute leukemias in aplasia and at high risk of early death (abstr.). *Haematologica* 1988, 73 (Suppl.), 41.
28. Muhn M, Andreeef M, Geissler K, *et al.* Rh GM-CSF in combination with chemotherapy—a new strategy in therapy of acute myeloid leukemia (abstr.). Third International symposium on minimal residual disease in acute leukemia, Rotterdam, 1990, 103.
29. Löwenberg B, Delwel R, Bot F, Budel L, Salem M, Touw I. Growth regulation of acute myeloid leukemia (AML) (abstr.) *Haematologica* 1988, **73** (Suppl), 17.
30. Clutterbuck R, Newman AA, Powles R, *et al.* Failure to immortalize human AML cells using human recombinant GM-CSF *in vitro* and *in vivo*. *Bone Marrow Transpl* 1989, **4**, (Suppl.), 40.
31. Riccardi A, Danova M, Wilson G, *et al.* Cell kinetics in human malignancies studied with in vivo administration of bromodeoxyuridine and flow cytometry. *Cancer Res* 1988, **48**, 6238–6245.
31. Riccardi A, Danova M, Wilson G, *et al.* Cell kinetics in human malignancies studied with in vivo administration of bromodeoxyuridine and flow cytometry. *Cancer Res* 1988, **48**, 6238–6245.
32. Girino M, Riccardi A, Danova M, *et al.* Immunocytochemical evaluation of proliferative activity in human brain tumours. *Anal Cell Pathol* (in press).
33. Girino M, Cuomo A, Danova M, Buttini R, Giordano M, Riccardi A. Ki 67 expression and BUDR-labeling index in acute non lymphoid leukemias (abstr.). *Cell Tissue Kinet* 1989, **22** (Suppl. 2), 133.

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Long-term Results of the HEAVD Protocol for Adult Acute Lymphoblastic Leukaemia

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Between 1979 and 1987, 82 adults (age 14–71 years) with acute lymphoblastic leukaemia (ALL) were treated with a 6-course protocol called HEAVD, the main feature of which was the early postremission administration of escalating doses of doxorubicin (total 405 mg/m^2) and cyclophosphamide (total 2.5 g/m^2). A complete remission (CR) was attained in 66 patients (80%, 95% confidence intervals, [CI] 71%–89%). Factors affecting favourable CR achievement were age < 60 years and absence of lymphadenopathy–hepatosplenomegaly at presentation ($P < 0.05$). Median duration of CR was 27 months. 26 patients remain in first continuous and unmaintained CR, 18 of whom between 5.9 and 11.1 years, for an estimated 39% prolonged disease-free survival (95% CI 27%–51%). CR duration correlated significantly with absolute blast cell count (15 × 10^9/l or less compared to more) and age (30 years or under compared to over). Overall, 29 patients are alive with a median follow-up of 6.7 years, the projected long term survival being 35% at 11 years (95% CI 24%–46%). Treatment-related toxicity included 1 lethal case of L-asparaginase-related thromboembolism and 3 toxic deaths among 66 CR patients. Late-onset toxicity was not observed in long-term survivors. The relatively late occurrence of endpoint events (relapse and death) in adult ALL confirms that long-term updating is necessary to determine the curative potential of modern chemotherapy programs for the disease.
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INTRODUCTION

ACUTE LYMPHOBLASTIC LEUKAEMIA (ALL) in adults is a rare and most often fatal neoplastic disease. Although as many as 80% of patients may initially achieve a complete remission (CR), most subsequently relapse and eventually die [1]. Since with modern treatment strategies a CR duration of 18–24 months is not unusual and systemic relapses occur as late as the fourth or fifth year of observation [1], clinical studies with a median follow-up period extended beyond 5 years are needed if the impact of a potentially curative therapeutic approach is to be properly assessed.

Starting in 1979, we have conducted an open uncontrolled study in adult ALL employing a regimen akin to HEAVD from St Bartholomew's Hospital (SBH, London, UK) [2],

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