Eur J Cancer Clin Oncol, Vol. 23, No. 11, pp. 1673–1678, 1987.
Printed in Great Britain

0277-5379/87$3.00+0.00

Idarubicin in Combination with Etoposide and Cytarabine in Adult Untreated Acute Non Lymphoblastic Leukemia

ANGELO M. CARELLA,* MARINA MARTINENGO,* GINO SANTINI,* EUGENIA GAOZZA,* EUGENIO DAMASIO,* DOMENICO GIORDANO,* SANDRO NATI,* ANGELA CONGIU,* RAFFAELLA CERRI,* MARCO RISSO,* FABRIZIO GANZINA† and ALBERTO M. MARMONT*

*Division of Hematology, Bone Marrow Transplantation Unit, Ospedale S. Martino, Genova, Italy and †Therapeutic Research Department, Farmitalia-C. Erba, Milano, Italy

Abstract—*Thirty-one unselected patients with untreated acute non lymphoblastic leukemia (ANLL) ranging in age from 15 to 76 years received two courses of a new high-dose induction regimen consisting of idarubicin, etoposide and cytarabine.*

Patients who entered complete remission (CR) were then allocated to post-remission intensification (PRI). Patients under 40 years of age with a HLA-compatible donor were given bone marrow transplantation (BMT); those without an HLA identical donor received either autologous BMT (ABMT) or no subsequent therapy.

Twenty-five out of 31 patients (80.6%) achieved CR (93.3% in young and 68.7% in old patients) and 14 (56%) after the first cycle. Six patients (five out six > 40 years) died of cerebral hemorrhage and/or infection during the induction phase and four additional patients (three elderly) died on the PRI for the same cause without recurrent disease. Eleven out 25 patients are disease-free survivors 2–34 months (median 10 months) after achievement of CR.

In conclusion, this intensive chemotherapy regimen is effective both in young and older patients but the post-remission intensification is too aggressive in elderly patients.

INTRODUCTION

THE IDENTIFICATION of new active drugs and their incorporation into combination chemotherapy protocols for the therapy of ANLL is a critical factor in the development of improved total therapy programs.

Idarubicin (4-demethoxydaunorubicin, 4-DMDR, IMI 30), a new derivative of daunorubicin, synthesized by Farmitalia-Carlo Erba, is one of the most promising new antileukemic agents studied over the last few years. This drug has been introduced in clinical studies on the basis of experimental data showing higher efficacy and higher therapeutic index than the parent structures [1–3].

In our first study, published elsewhere [4–6], 4-DMDR was studied in 35 pretreated acute leukemia patients. We now report our experience with 4-DMDR in combination with etoposide (VP-16) and cytarabine (ARA-C) in patients treated at the onset of their disease.

Accepted 23 June 1987.
Address reprint requests to A.M. Carella, Divison of Hematology, Ospedale S. Martino, Viale Benedetto XV, Genova, Italy.
Supported by Associazione Italiana Ricerca sup Cancro (A.I.R.C.)

MATERIALS AND METHODS

Objectives

The objectives of this clinical trial were: (a) to determine the effectiveness of this combination in inducing complete remission (CR); (b) to evaluate CR duration and tolerability after a PRI, followed by supramaximal therapy and BMT or ABMT (according to the availability or not of a histocompatible donor for the patients among their siblings); (c) to evaluate the cardiac and non-cardiac toxicity.

Patients

Thirty-one previously untreated ANLL patients (17 males and 14 females) entered this study. There was no selection process involved in the admission of patients to this trial. None of these patients had developed ANLL following treatment for a prior malignancy. Mean and median age were 40 and 46, respectively (range 15–76 years). The distribution of patients by FAB classification [7] included M1: 9; M2–M3: 7; M4–M5: 15 patients. Specimens for cytogenetic studies were obtained from the bone marrow of 20 patients; 10 were tested

successfully. Seven (70%) had chromosomal abnormalities: two were pseudodiploid, four were hyperdiploid and one was hypodiploid.

Treatment

Remission–induction therapy for all patients consisted of intravenous 4-DMDR at a dose of 8 mg/m^2 for 3 days, VP-16 at 150 mg/m^2 in 2 h infusion for 3 days and ARA-C at 200 mg/m^2 in continuous infusion for 5 days (3+3+5 protocol). The second course was given using the same doses, except that 4-DMDR was administered for only 2 days.

CR was defined according to criteria of Cancer and Leukemia Group B [55]. Patients who achieved CR received a PRI. This therapy was given 2–4 weeks after CR achievement and consisted of four courses of 4-DMDR (10 mg/m^2 i.v. day 1), ARA-C (60 mg/m^2 every 8 h, days 1–5) and 6-thioguanine (70 mg/m^2 every 8 h orally days 1–5). The 2nd, 3rd and 4th courses were given after neutrophils and platelets were $\geq$ 1000/mmc and $\geq$ 100,000/mmc, respectively; besides, all these drugs were utilized at the same doses as above except for ARA-C which was administered at 80 mg/m^2 on the 2nd course, 110 mg/m^2 on the 3rd and 150 mg/m^2 on the 4th course.

Once PRI was completed, the patients under 40 years with an HLA-compatible donor in continuous CR were given a BMT; the others received autologous BMT or no further therapy.

Conditioning for BMT and ABMT

All these cases received cyclophosphamide 60 mg/kg/day on two successive days followed by fractionated total body irradiation (3.3 Gy × 3 days) (BMT) or single dose TBI (10 Gy) (ABMT).

The day after TBI, the marrow cells of donor or non-'purged' cryopreserved autologous cells were given to the patients. All other BMT procedures such as care of patients, prophylaxis of graft versus host disease with cyclosporin A etc. have been extensively described [8].

Supportive therapy

Transfusions of blood and platlets were given when required. Human leucocyte antigen (HLA) matched platelets were given to patients unresponsive to random platelet transfusions. Patients were kept in conventional hospital rooms and received oral non-absorbable antibiotics for gut decontamination. Infectious complications were treated with aminoglicosides and cephalosporins plus high-dosage immunoglobulins, always with mepartricin as an antifungal therapy.

Criteria for toxicity

Toxicity severity was graded according to a five grade system from 0 to 4 [56].

Pharmaceutical data on 4-DMDR

4-DMDR was supplied by Farmitalia-Carlo Erba Research Laboratories, Milan (Italy), in sterile vials for intravenous administration containing 5 mg of 4-DMDR, as a red-orange lyophilized powder. The drug was reconstituted in 5 ml of sterile water for injection and administered by intravenously over 5 min.

RESULTS

The results, as of October 1986, are summarized in Table 1. All transplanted patients were included in the evaluation of remission duration time of withdrawal from the study.

Among the 31 patients, 25 (80.6%) had a CR (93.3% in young and 68.7% in old patients) and 14 (56%) after only the first course. Eleven out of 25 patients (44%) remained in continuous CR 2–34 months (median 10 months). There were six deaths during induction and four deaths during PRI for disseminated bacterial complications and/or cerebral hemorrhage (eight out of 10 patients were old); one patient died after ABMT for cerebral hemorrhage and another patient relapsed and died after BMT. Twelve patients relapsed in the bone marrow 2–9 months (median 5 months) after achievement of CR (Fig. 1). No significant prognostic factors for disease-free survival in this group were identified in a multivariated analysis that included FAB classification, WBC count, age and sex.

Toxicity

In all patients severe reductions in granulocytes and platelets occurred within 7–10 days from completing induction chemotherapy. Greater than 80% of induction courses were associated with fever $\geq$ 39° C. The fever in neutropenic patients ($\leq 0.5 \times 10^9$/l) was assumed to be related to infections and was treated with systemic antibiotics in combination with antifungal therapy. No patient received prophylactic granulocyte transfusions. Infections occured rarely during PRI, except for elderly patients, in whom the fever, always associated with documented gram-negative septicemia, was present greater than 70% of four PRI courses. All patients had platelet count $\leq 20 \times 10^9$/l with a median duration of 14 days (range 10–20) after induction therapy. Bleeding occured frequently during induction in elderly patients while this complication was present less frequently in PRI phase.

The non-hematologic toxicities are summarized in Table 2; briefly, moderate nausea and vomiting, alopecia and liver dysfunction were the toxicities most frequently observed.

Table 1. *Results of* 3+3+5 *protocol for ANLL patients*

Patients	31
Age/sex	
15–48 years	15 (males: 10; females: 5)
49–76 years	16 (males: 7; females: 9)
Induction failures	—
Induction deaths	6
≥ 49 years	5
≤ 48 years	1
Complete remission	25/31 (80.6%)
15–48 years	14/15 (93.9%)
49–76 years	11/16 (68.7%)
Complete remission after first course	14/25 (56%)
BMT	3 patients
ABMT	5 patients (one died of cerebral hemorrhage)
PRI deaths	4
≥ 49 years	3
≤ 48 years	1
Relapses	12 (one after BMT and two after ABMT)
Continuous remissions	11/25 patients (44%)
Median CR duration (months)	10 (range: 2–34)

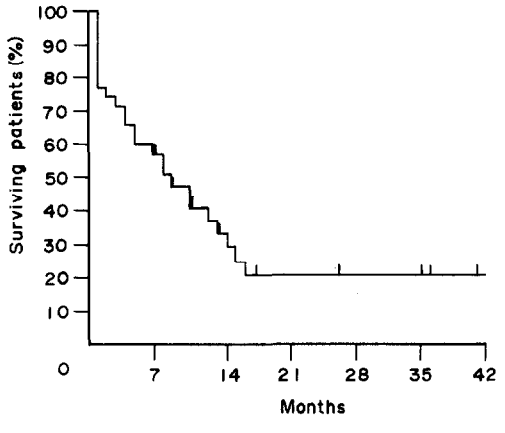

Fig. 1. *Actuarial survival in* 31 *ANLL patients treated with* 3+3+5 *protocol.*

Table 2. *Toxicity in* 31 *patients treated with* 3+3+5 *protocol (NCOG criteria)*

	0	1	2	3	4	Fatal
Nausea and vomiting		9	12	10		
Alopecia				31		
Mucositis	19	7	2	3		
Diarrhea	22	3	4	2		
Liver toxicity	18	5	5	2	1	
Infection		1	14	12		4
Bleeding	9	2	8	5	1	6
Cardiac toxicity	30	1*				

*This case had had cardiac ischemia before inductive therapy.

DISCUSSION

The recent advances in oncolytic therapy and supportive care, which enable the patient to survive the inevitable aplastic phase from the inductive therapy, resulted in a significant progress in the CR rates and in the prognosis of acute leukemia patients. To date, first-line chemotherapy can produce CR in 60–80% of previously untreated adults with ANLL [10–13] and can cure 10–20% of them [14]. These high CR rates, however, have not been associated with proportional increase of CR duration and indefinite survival, except for patients who underwent BMT [15, 16] or ABMT [17].

No definite conclusion has been obtained from 'maintenance' treatment. According to some authors this procedure extends the median CR duration from 10 to 17 months [18–22] compared to 5–8 months when no post-remission treatment is given [23–25]. Moreover, recent clinical trials suggest that it is possible to extend the CR duration from 20–25% to 40% or more if the patients receive the PRI precociously in first CR [12, 25–34]. It is also uncertain whether the additional low-dose maintenance treatment will lead to any further benefit [33, 35].

Following our and other published clinical experiences of 4-DMDR [36–48], we decided to evaluate a new therapeutic protocol in untreated ANLL patients. The pilot study described here indicated that a CR rate of 80.6% has been achieved (93.3% CR in young and 68.7% in old patients) and that 56% of patients obtained the CR after only the first course.

Notwithstanding the intensity of PRI, only four, among the not transplanted, young patients, are alive and well in their CR; another four young patients are in continuous CR but received ABMT or BMT. The last three patients achieved first

complete remission but have not yet begun PRI. All other patients relapsed precociously or died of septicemic complications and/or cerebral hemorrhage during PRI (three out four were old patients). These results confirm the fragility of the elderly patients to aggressive chemotherapy mainly due to development of septicemia and brain bleeding but we have not observed the cardiac complications seen by others with DNR [14, 49, 50]. Although some recent studies have reported high response rates in elderly patients receiving intensive chemotherapy, the administration of this treatment in elderly leukemic patients still remains controversial [26, 50]. Foon *et al.* treated 107 patients with a single intensive induction chemotherapy regimen [52]. Patients 60 years and older had the same remission rate as the younger patients. Furthermore, median remission duration, median survival and projected long-term survival were comparable between the two groups. Although recent trials have suggested that the PRI increase the median CR duration [53, 54], in our experience this was not evident not only in old but also in young patients; the sole continuous CR patients being those who have been treated in first CR with a bone marrow transplant program.

In conclusion, although still preliminary, our data confirm that the combination of 4-DMDR, VP-16 and ARA-C is a highly effective primary therapy for inducing CR in patients with previously untreated ANLL and that most patients can enter a CR after the first course. The non-hematologic toxicity of this regimen is within the expected limits in young patients, while it was too aggressive in elderly patients even if no cardiac toxicity was observed. In our hands the PRI not only did not determine an increase of continuous CR but caused an increase of toxicity in elderly patients.

REFERENCES

1. Arcamone FL, Bernardi L, Giordano RP. Synthesis and antitumor activity of 4-DMDR and their beta anomers. *Cancer Treat Rep* 1976, **60**, 829–834.
2. Casazza AM, Bertazzoli C, Pratesi G, Bellini O, Di Marco A. Antileukemic activity and cardiac toxicity of 4-DMDR in mice. *Proc Am Assoc Cancer Res* 1979, **20**, 16 (Abstract).
3. Casazza AM, Pratesi G, Giuliani F, Di Marco A. Antileukemic activity of 4-demethoxydaunorubicin in mice. *Tumori* 1980, **66**, 549–564.
4. Carella AM, Santini G, Nati S *et al.* Phase II trial of idarubicin in 16 refractory or relapsed acute leukemia patients. 4th NCI-EORTC Symposium on New Drugs in Cancer Therapy, Brussels, Belgium, 1983, Proceedings Abstract.
5. Carella AM, Santini G, Marmont AM. 4-Demethoxydaunorubicin (idarubicin) in refractory or relapsed acute leukemias. *Haematologica* 1984, **69**, 767–768.
6. Carella AM, Santini G, Martinengo M *et al.* 4-Demethoxydaunorubicin (idarubicin) in refractory or relapsed acute leukemias. A pilot study. *Cancer* 1985, **55**, 1452–1454.
7. Bennet JM, Catovsky D, Daniel MT *et al.* Proposals for the classification of acute leukemias. *Br J Haematol* 1976, **33**, 451–458.
8. Bacigalupo A, Frassoni F, Van Lint MT *et al.* Bone marrow transplantation for acute nonlymphoid leukemia (ANLL) in first remission. *Acta Haematol* 1985, **74**, 23–26.
9. Kaplan EL, Meier P. Non parametric estimation from incomplete observation. *J Am Stat Assoc* 1958, **53**, 457–481.
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, **i**, 786–788.
11. Mayer RJ, Schiffer CA, Peterson BA *et al.* Intensive post-remission therapy in adults with acute nonlymphocytic leukemia with ARA-C by continuous infusion or bolus administration: preliminary results of a CALGB phase I study. *Semin Oncol* 1985, **2**, 84–90.
12. Preisler HD, Raza A, Rustum Y, Browman G. The treatment of lymphocytic leukemia in remission. *Semin Oncol* 1985, **12**, 91–97.
13. Keating MJ, Smith TL, Gehan EA *et al.* Factors related to length of complete remission in adult acute leukemia. *Cancer* 1980, **45**, 2017–2029.
14. Keating MJ, Smith TL, McCredie KB *et al.* A four-year experience with anthracycline, cytosine arabinoside, vincristine and prednisone combination chemotherapy in 325 adults with acute leukemia. *Cancer* 1981, **47**, 2779–2788.
15. Zwaan FE, Hermans J, Barret AJ, Speck B. Bone marrow transplantation for acute non lymphoblastic leukemia: a survey of the European Group for Bone Marrow Transplantation. *Br J Haematol* 1984, **56**, 645–653.
16. Thomas ED, Buckner CD, Clift RA *et al.* Marrow transplantation for acute non lymphoblastic leukemia. *N Engl J Med* 1979, **301**, 597–599.
17. Gorin NC, Aegerter P. Autologous bone marrow transplantation for acute leukemia in remission: Third European Survey: March 1986. *Bone Marrow Transplantation* 1986, **1** (suppl.1), 255–258.
18. Gale RP, Foon KA, Cline MJ. Intensive chemotherapy for acute myelogenous leukemia. *Ann Intern Med* 1981, **94**, 753–757.
19. Rai KR, Holland JF, Glidewell OJ. Treatment of acute myelocytic leukemia: a study by Cancer and Leukaemia Group B. *Blood* 1981, **50**, 1203–1212.

20. Passe S, Mike V, Mertelsmann R. Acute non lymphoblastic leukemia. Prognostic factors in adult with long-term follow-up. *Cancer* 1982, **50**, 1462–1471.
21. Peterson BA, Bloomfield CD. Long-term disease-free survival in acute non-lymphocytic leukemia. *Blood* 1981, **57**, 1144–1147.
22. Yates J, Glidewell O, Wiernik P. Cytosine arabinoside with daunorubicin or adriamycin for therapy of acute myelocytic leukemia: a CALGB study. *Blood* 1982, **60**, 454–462.
23. Embury SH, Elias L, Hellr PH. Remission maintenance therapy in acute myelogenous leukemia. *West J Med* 1981, **126**, 267–272.
24. Lewis JP, Pajak PF, Linman JW. Maintenance management of acute non-lymphocytic leukemia. *Cancer Clin Trials* 1981, **4**, 115–124.
25. Vaughn WP, Karp JE, Burke PJ. Two-cycle timed-sequential chemotherapy for adult acute non lymphocytic leukemia. *Blood* 1984, **64**, 975–980.
26. Rees JKH, Gray RG, Swirsky D, Hayhoe FGJ. Principal results of the Medical Research Council's 8th Acute Myeloid Leukemia Trial. *Lancet* 1986, **ii**, 1236–1241.
27. Weintein HJ, Mayer RJ, Rosenthal DS. Chemotherapy for acute myelogenous leukemia in children and adults: VAPA update. *Blood* 1983, **62**, 315–319.
28. Hines JD, Mazza JJ, Oken MM *et al.* High-dose cytosine arabinoside and m-Amsa induction and consolidation in patients with previously untreated *de novo* acute nonlymphocytic leukemia: phase I pilot study for the Eastern Cooperative Oncology Group. *Semin Oncol* 1985, **12**, 117–119.
29. Champlin R, Jacobs A, Gale RP. Prolonged survival in acute myelogenous leukemia without maintenance therapy. *Lancet* 1984, **1**, 984–986.
30. Cassileth P, Begg C, Bennet J. Intensive consolidation therapy with high-dose of cytosine arabinoside and m-Amsa in adults with acute non lymphoblastic leukemia (ANLL). *Proc Am Soc Clin Oncol* 1984, **C-754**, 3 (Abstract).
31. Bell R, Rohatiner AZS, Slevin ML. Short-term treatment for acute myelogenous leukemia. *Br Med J* 1982, **284**, 1221–1224.
32. Preisler HD, Breecher M, Browman G *et al.* The treatment of acute myelocytic leukemia in patients 30 years of age and younger. *Am J Hematol* 1982, **13**, 189–198.
33. Saunter C, Berchtold W, Fopp M *et al.* Acute myelogenous leukemia maintenance chemotherapy after consolidation treatment does not prolong survival. *Lancet* 1984, **i**, 379–382.
34. Bernasconi C, Lazzarino M, Morra E *et al.* Intensive post-remission consolidation chemotherapy for acute myeloid leukemia (AMLL) in adults. *Leukemia Res* 1986, **10**, 108 (Abstract).
35. Jacobs P, Dubovsky DM, Wood L. In adult non lymphoblastic leukemia, extended maintenance chemotherapy has no benefit. *Am J Hematol* 1984, **16**, 255–265.
36. Berman E, Arlin Z, Daghestani I, Gee S, Kempin S, Mertelsmann R. Phase I–II study of idarubicin and cytarabine in acute leukemia. *Proc Am Assoc Cancer Res* p. 187, Toronto (Abstract) 1984.
37. Daghestani AN, Arlin ZA *et al.* Phase I–II clinical and pharmacology study of 4-demetoxydaunorubicin (idarubicin) in adult patients with acute leukemia. *Cancer Res* 1984, **45**, 1408–1412.
38. Young CW, Arlin ZA, Daghestani AN, Schulman P, Leyland-Jones B. Phase I and phase II evaluation of 4-demethoxydaunorubicin in acute leukemia. Proceedings of 13th International Congress of Chemotherapy, Vienna, Abstract, 1983, 48–50.
39. Lambertenghi-Deliliers GI, Pogliani E, Maiolo AT, Pacciarini MA, Stegnjaich S, Piazza E. Human pharmacokinetic studies on three new anthracyclines: epirubicin, idarubicin, esorubicin. Fourth NCI-EORTC Symposium on New Drugs in Cancer Therapy, Brussels, Belgium, Proc., Abstract, Dec. 1983.
40. Bandini G, Scapoli G, Leoni F *et al.* Effect of 4-demethoxydaunorubicin (4-DMDR) in chronic myeloid leukemia in blastic transformation and relapsed acute leukemias. *Haematologica* 1985, **70**, 155–159.
41. Carella AM, Santini G, Giordano D *et al.* Idarubicin alone or in combination with cytarabine and etoposide (3+3+5 protocol) in acute non lymphoblastic leukemia. *Leukemia Res* 1985, **9**, 631–632.
42. Steinherz L, Hoffman N, Steinherz P *et al.* Evaluation of cardiac effects of 4-demethoxydaunorubicin (DMDR) in children. *Proc Am Soc Clin Oncol* 1983, **2**, 69.
43. Tan C, Bacha D, Hancock C. New anthracyclines in childhood cancer. Communication at International Congress of Chemotherapy, Kyoto, June 1985.
44. Madon E, Carli M, Ceci A *et al.* Phase II study of idarubicin (4-demethoxydaunorubicin) in pediatric acute leukemias and solid tumors. Communication at 3rd European Conference on Clinical Oncology, Stockholm, June 1985.
45. Mandelli F, Testi AM, Aloe Spiriti MA *et al.* Evaluation of polychemotherapeutic schedule including 4-demethoxydaunorubicin in relapsed acute lymphocytic leukemia. *Haematologica* 1986, **71**, 34–38.
46. Ganzina F, Pacciarini MA, Di Pietro N. Idarubicin (4-demethoxydaunorubicin). A preliminary overview of preclinical and clinical studies. *Invest New Drugs* 1986, **4**, 85–105.
47. Lambertenghi-Deliliers G, Maiolo AT, Annaloro C, Pogliani E, Baldini L, Polli EE. Complete remission in prolymphocytic leukemia with 4-DMDR and arabinosyl-cytosine. *Cancer* 1984, **54**, 199–201.

48. Eridani S, Slater NGP, Singh AK, Pearson TC. Intravenous and oral demethoxydaunorubicin (NSC 256-439) in the treatment of acute leukemia and lymphoma: a pilot study. *Blut* 1985, **54**, 199–201.
49. Bern MM, Cloud LP, Corkey JC *et al.* Age and treatment of acute non lymphoblastic leukemia. *N Engl J Med* 1981, **305**, 642–643.
50. Naparstek E, Zajicek G, Or R, Rachmilewits EA, Elias M, Polliack A. Results of therapy in adult acute non lymphoblastic leukemia: experience in Jerusalem, Israel, during 1975–1982. *Acta Haematol* 1985, **73**, 11–15.
51. Mayer RJ, Weinstein JH, Coral FS, Rosenthal DS, Frei E. The role of intensive chemotherapy in the management of patients with acute myelogenous leukemia. *Cancer Treat Rep* 1982, **66**, 1455–1462.
52. Foon KA, Zighelboim J *et al.* Intensive chemotherapy in the treatment of choice for elderly patients with acute myelogeous leukemia. *Blood* 1981, **58**, 467–469.
53. Casseleth PA, Katz ME. Chemotherapy for adults: acute non lymphocytic leukemia with daunorubicin and cytosine arabinoside. *Cancer Treat Rep* 1977, **61**, 1441–1445.
54. Peterson BA, Bloomfield CD. Treatment of acute non lymphocytic leukemia in elderly patients. *Cancer* 1977, **40**, 647–652.
55. Ellison RR, Holland JF, Weil M *et al.* Arabinsoyl-cytosine: a useful agent in the treatment of acute leukemia in adults. *Blood* 1968, **32**, 507–532.
56. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1981, **47**, 207–214.