original paper
*Haematologica 1997; 82:660-663*

# IDARUBICIN AND CYTOSINE ARABINOSIDE IN THE INDUCTION AND MAINTENANCE THERAPY OF HIGH-RISK MYELODYSPLASTIC SYNDROMES

ROSANGELA INVERNIZZI, ALESSANDRO PECCI, GIUSEPPE ROSSI,* ANNA MARIA PELIZZARI,*
MARCELLO GIUSTO, CARMINE TINELLI,° EDOARDO ASCARI
*Medicina Interna ed Oncologia Medica, Università di Pavia e °Unità di Biometria, IRCCS Policlinico S.Matteo, Pavia; *Sezione di Ematologia, Spedali Civili, Brescia, Italy*

**ABSTRACT**

**Background and Objective.** Recently, the results of some pilot studies have shown the efficacy of the association of idarubicin (IDA) and cytosine arabinoside (Ara-C), already successfully employed in acute myeloid leukemia (AML), for remission induction in patients with myelodysplastic syndrome (MDS). We set out to evaluate in a multicenter study the efficacy and tolerability of an intensive therapy with IDA and Ara-C in patients with RAEB and RAEB-t, the rate and duration of complete remission, and the overall survival in adults treated with full doses and in the elderly treated with lower doses; furthermore, we investigated the efficacy of low-dose maintenance chemotherapy.

**Methods.** Pretreated adult patients with *de novo* RAEB and RAEB-t, meeting at least one of the following criteria, were included: neutrophils $< 0.5\times10^9$/L or moderate neutropenia with infectious episodes, platelets $< 30\times10^9$/L or moderate thrombocytopenia with bleeding symptoms, transfusion > 4 red cell units/months, rapid increase of bone marrow blasts. Induction treatment consisted of a cycle with IDA and Ara-C. Adult patients less than 65 years old were treated with the following doses: Ara-C 1 g/m$^2$/day i.v. 6-hour infusion, on days 1-4, IDA 10 mg/m$^2$/day i.v., on days 1-3. Elderly patients (≥65 yrs) were treated with lower doses: Ara-C 1 g/m$^2$/day 6 hours infusion, on days 1 and 2, IDA 10 mg/m$^2$/day i.v., on days 1 and 2. Responders followed a consolidation course identical to induction.

**Results.** From February 1994 to February 1997, 25 patients were enrolled, 20 males and 5 females aged between 22 and 76, 10 were ≥ 65 years old, 7 had RAEB and 18 had RAEB-t. Twelve cases (48%) achieved complete remission (CR), 7 cases (28%) achieved partial remission, 4 patients were resistant and two patients (8%) died during the aplastic phase. A significantly higher CR rate was found in younger patients (p = 0.036), while gender, FAB subtype, presence of Auer rods, cytogenetic findings, and the interval from diagnosis to treatment did not significantly influence CR achievement.

**Interpretation and Conclusions.** Our results show that in *de novo* RAEB and RAEB-t, treatment with IDA and Ara-C is associated with satisfactory frequency of response with acceptable toxicity.


*Key words: acute myeloid leukemia, chemotherapy, idarubicin, cytosine arabinoside*

Prognosis in patients with myelodysplastic syndrome (MDS) and a high percentage of bone marrow blasts is very poor: according to the reports of the largest numbers of cases published in the last decade, median survival rates of patients with refractory anemia with excess of blasts (RAEB) and RAEB in transformation (RAEB-t) are 13 and 6 months, respectively.[1]

The lack of randomized clinical trials does not allow for the definition of guidelines for therapy of RAEB and RAEB-t; furthermore, the relative efficacy of the various treatment approaches is not clear, nor are their advantages in comparison with supportive therapy alone. The only strategy capable of prolonging survival significantly is allogeneic or autologous bone marrow transplantation.[2] For patients aged between 55 and 65, intensive chemotherapy is the most efficacious treatment. In fact, complete remission (CR) can be reached in about 60% of cases; it lasts, however, only about 10 months and less than 10% of cases are disease-free at 3 years.[3,4]

Recently, the results of some pilot studies have shown the efficacy of the association of idarubicin (IDA) and cytosine arabinoside (Ara-C), already successfully employed in acute myeloid leukemia (AML), for remission induction in patients with MDS.[5-9] The lower cardiotoxicity of IDA compared to other anthracyclines, and a reduction of Ara-C doses made the treatment feasible and well tolerated even in elderly patients.

°*This paper also appeared in Haematologica supplement to issue n. 5, 1997 (symposium supplement).*
*Correspondence: Dr. Rosangela Invernizzi, Internal Medicine and Medical Oncology, IRCCS Policlinico S. Matteo, 27100 Pavia, Italy. Tel. international +39.382.502956. Fax. international +39.382.526223.*
*Received July 24, 1997; accepted September 25, 1997.*

We set out to evaluate in a multicenter study the efficacy and tolerability of an intensive therapy with IDA and Ara-C in patients with RAEB and RAEB-t, the rate and duration of CR, and the overall survival in adults treated with full doses and in the elderly treated with lower doses; furthermore, we investigated the efficacy of low-dose maintenance chemotherapy.

## Patients and Methods

*Patients*

Pretreated adult patients with *de novo* RAEB and RAEB-t meeting at least one of the following criteria, were included: neutrophils $<0.5\times10^9$/L or moderate neutropenia with infectious episodes, platelets $< 30\times10^9$ or moderate thrombocytopenia with bleeding symptoms, transfusion > 4 red cell units/months, rapid increase of bone marrow blasts.

Criteria for exclusion were the following: presence of documented infection, asymptomatic disease with stable hematological values, performance status > 2 according to the WHO scale, severe heart failure and/or severe arrhythmias, inadequate liver or renal function, and patients already treated by intensive chemotherapy and/or radiotherapy for previous neoplasms.

Informed consent was obtained from all patients.

*Design of the protocol*

Induction treatment consisted of a cycle with IDA and Ara-C; adult patients less than 65 years old were treated with the following doses: Ara-C 1 g/m$^2$/day i.v. 6-hour infusion, on days 1-4, IDA 10 mg/m$^2$/day i.v., on days 1-3; elderly patients (≥ 65 yrs) were treated with lower doses: Ara-C 1 g/m$^2$/day i.v. 6-hour infusion, on days 1, 2, IDA 10 mg/m$^2$/day i.v., on days 1 and 2. Responders followed a consolidation course identical to induction. Patients in CR after consolidation regimen had to be treated for 2 years with maintenance therapy consisting of alternate cycles of Ara-C 10 mg/m$^2$ s.c. every 12 hours for 10 days a month, and IDA 15 mg/m$^2$/day p.o. for 3 days a month.

Complete remission was defined as normocellular bone marrow with less than 5% blasts and at least $1.0\times10^9$/L neutrophils and $100\times10^9$/L platelets in the peripheral blood. Partial remission (PR) was defined as a 50% or more reduction of blasts in a normocellular marrow.

*Statistics*

Actuarial curves were calculated according to the method of Kaplan-Meier. The differences between curves were statistically tested using the two-tailed log-rank test. Comparisons of some parameters for their prognostic value were performed with the Fisher exact test. The duration of survival was calculated from the date of starting treatment until death. For patients who achieved CR, the disease-free survival (DFS) was calculated from the date of first CR to the date of relapse, death in CR or the most recent follow-up.

**Table 1. Characteristics of the patients.**

| | |
|---|---|
| Total patients | 25 |
| M/F | 20/5 |
| Age | |
| *median (range)* | 61 (22-76) |
| *≥ 65 yrs* | 10 |
| RAEB/RAEB-t | 7/18 |
| Interval from diagnosis | |
| *< 3 months* | 20 |
| *≥ 3 months* | 5 |
| Karyotype | |
| *normal* | 9 |
| *abnormal* | 12 |
| Hb g/dL | |
| *median (range)* | 8.8 (4.5-12.8) |
| Neutrophils x $10^9$/L | |
| *median (range)* | 0.95 (0.01-6.49) |
| Platelets x $10^9$/L | |
| *median (range)* | 46 (8-260) |

**Table 2. Response to therapy.**

| | *Total* | *< 65 years* | *> 65 years* |
|---|---|---|---|
| Patients | 25 | 15 | 10 |
| Complete remission | 12 (48%) | 10 (67%) | 2 (20%) |
| Partial remission | 7 (28%) | 2 (13%) | 5 (50%) |
| No remission | | | |
| *Death in aplasia* | 2 (8%) | 1 (7%) | 1 (10%) |
| *Resistant* | 4 (16%) | 2 (13%) | 2 (20%) |
| Median survival (months) | 12 | 21 | 5 |

## Results

From February 1994 to February 1997, 25 patients were enrolled, 20 males and 5 females aged between 22 and 76, 10 were ≥ 65 years old, 7 had RAEB and 18 had RAEB-t. Their clinical and hematological features are summarized in Table 1. In 5 cases, treatment was started more than 3 months after diagnosis.

Twelve cases (48%), 2 RAEB and 10 RAEB-t, 2 ≥ 65 years old achieved CR; 7 cases (28%), 5 ≥ 65 years old achieved PR; 4 patients (16%), 2 ≥ 65 years old were resistant to therapy (Table 2). A significantly higher CR rate was found in younger patients (p=0.036), while gender, FAB subtype,

**Table 3. Toxicity of chemotherapy (> grade 1 WHO).**

| | *Induction course* | *Consolidation course* | *Maintenance course* |
|---|---|---|---|
| No. of evaluable cases | 25 | 18 | 11 |
| Infection/FUO | 11/13 | 3/5 | 0/2 |
| Hemorrhage | 9 | 6 | 0 |
| Gastrointestinal | 5 | 2 | 0 |
| Hepatic | 2 | 2 | 1 |
| Cardiovascular | 3 | 1 | 0 |
| Alopecia | 9 | 5 | 1 |

**Table 4. Supportive therapy.**

| | *Induction course* | *Consolidation course* |
|---|---|---|
| Platelet units (mean±se) | | |
| *Apheresis* | 3.1±1.6 | 1.2±0.7 |
| *Random* | 20.5±8.4 | 11.5±3.8 |
| Erythocyte units (mean±se) | 9.4±1.7 | 8.0±1.9 |

presence of Auer rods, cytogenetic findings, and the interval from diagnosis to treatment did not significantly influence CR achievement. Two patients (8%) died during the aplastic phase, one from sepsis and one from cerebral hemorrhage, aged 57 and 66, respectively. Complications of chemotherapy as well as supportive therapy are summarized in Tables 3 and 4.

Among CR patients, median times to recovery of neutrophils ($1\times10^9$/L) and platelets ($100\times10^9$/L) were, respectively, 21 (range 16-24) and 18 (range 14-28) days. No severe complications occurred during consolidation and maintenance courses.

The median duration of DFS was 18 months. The median survival duration of patients achieving CR was 21 months, while it was only 5 months in the PR and resistant patients (p=0.002); median survival for the whole population was 12 months (Figure 1). Survival duration was significantly (p=0.043) longer in patients with normal karyotypes (median 21 months) compared to patients with cytogenetic anomalies (median 11 months). Eight patients are still living, 7 of whom are in continuous CR, which in 3 cases has lasted for more than 19 months.

## *Discussion*

Since the early eighties, according to the schedules commonly used for acute leukemia, intensive chemotherapy has been employed for the treatment of high risk MDS, with the aim of eradicating the pathological clone, allowing for the recovery of normal hematopoiesis.[10,11] Lack of randomized trials, however, does not yet allow for the evaluation of the real efficacy of this kind of treatment, nor of its advantages in comparison with supportive therapy alone. Furthermore, the interpretation of the results of the studies already published is difficult for other reasons:groups of patients are small, FAB subtype is not specified, both primary and secondary cases, almost always in leukemic progression as well, are included.[3,4]



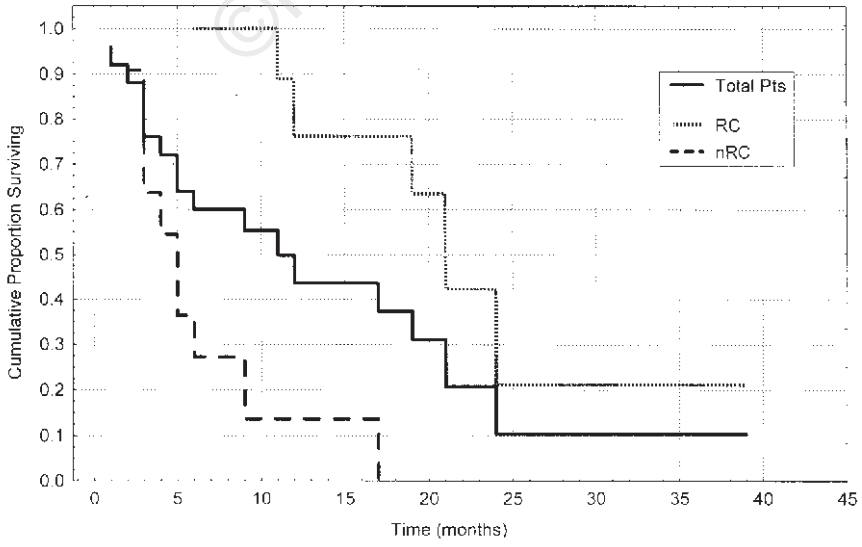


**Figure 1. Actuarial survival curves of all patients, of patients achieving CR and of patients not achieving CR.**

Generally, combinations of anthracyclines and Ara-C at standard or high doses, with or without thioguanine, have been used.[5,6,8,12-14] CR rates were variable, ranging from 15% to 80%, but they were usually lower than in *de novo* acute leukemia.[7,8,11,14,15] The most important reasons for this phenomenon are the generally older age of patients with MDS, as well as peculiar biological characteristics of the dysplastic clone, namely, the increased expression of chemoresistance proteins and the higher incidence of complex cytogenetic anomalies.[16,17] In fact, if such prognostic factors are compared, the results of treatment are similar in *de novo* AML and in MDS.[17]

Cytopenias are long with a high incidence of toxic deaths (14-25%), generally due to infections. The duration of remission and survival, ranging from 6 to 12 months and from 9 to 18 months, respectively, is shorter than in *de novo* AML.[8,10,14,18,19]

We performed a prospective multicenter study of intensive chemotherapy for patients with RAEB and RAEB-t, in good clinical conditions, with serious or symptomatic cytopenia. Our protocol consisted of induction and consolidation regimens with IDA and Ara-C, and maintenance cycles with the same drugs at low doses. Idarubicin was used in consideration of its lower cardiotoxicity compared to other anthracyclines and its pervious documented efficacy against blasts expressing high drug resistance.

Our results show that in *de novo* RAEB and RAEB–t, this combination regimen is associated with a satisfactory frequency of response with acceptable toxicity. In fact, 76% of our patients achieved CR or PR, while the therapy-related mortality was rather low. Only a complete response, however, significantly influenced the duration of survival. These data support the results of other recent studies;[8,14,18,19] in patients less than 65 years old, the CR rate (67%) reported by us was even higher than those described by other authors using similar regimens but excluding elderly patients. Therefore, intensive chemotherapy is certainly indicated in young patients with high risk MDS, although those cases are only a minority of the whole MDS patient population.[20] The use of full dose therapy in the elderly as well may increase their rather low CR rate, since no other prognostic factors were found to influence the achievement of remission.

Finally, although the short follow-up period does not allow for definitive conclusions, the fact that the CR duration of our patients was slightly longer than those reported by other authors suggests that maintenance therapy may prolong the period of CR and survival. It remains to be seen whether autologous stem cell transplantation can improve the outcome of CR in MDS patients as it does in AML patients.[21] A limiting factor for this procedure, however, might be a low number of normal residual stem cells.

## References


1. Gallagher A, Darley RL, Padua R. The molecular basis of myelodysplastic syndromes. Haematologica 1997; 82:191-204.
2. Aglietta M, De Vincentiis A, Lanata L, et al. Peripheral blood stem cells in acute myeloid leukemia: biology and clinical applications. Haematologica 1996; 81:77-92.
3. Cheson BD. Chemotherapy and bone marrow transplantation for myelodysplastic syndromes. Semin Oncol 1992; 19:85-94.
4. Gassmann W, Schmitz N, Loeffler H, De Witte T. Intensive chemotherapy and bone marrow transplantation for myelodysplastic syndromes. Semin Hematol 1996; 33:196-205.
5. Ganser A, Heil G, Kolbe K, et al. Aggressive chemotherapy combined with G-CSF and maintenance therapy with interleukin-2 for patients with advanced myelodysplastic syndrome, subacute or secondary acute myeloid leukemia. Ann Hematol 1993; 66:123-5.
6. Hoffmann K, Flasshove M, Fricke HJ, et al. Therapy of advanced myelodysplastic syndrome (MDS) with cytarabine and idarubicin (AIDA). Proc Am Soc Clin Oncol 1995; 14:335.
7. Estey EH, Kantarjian H, Keating M. Idarubicin plus continuous-infusion high-dose cytarabine as treatment for patients with acute myelogenous leukemia or myelodysplastic syndrome. Semin Oncol 1993; 20(suppl 8):1-5.
8. De Witte T, Suciu S, Peetermans M, et al. Intensive chemotherapy for poor prognosis myelodysplasia (MDS) and secondary acute myeloid leukemia (sAML) following MDS of more than 6 months duration. A pilot study by the Leukemia Cooperative Group of the European Organisation for Research and Treatment in Cancer (EORTC-LCG). Leukemia 1995; 9:1805-11.
9. Bassan R, Barbui T. Remission induction therapy for adults with acute myelogenous leukemia: towards the ICE age? Haematologica 1995; 80:82-90.
10. Mertelsmann R, Thaler HT, To L, et al. Morphological classification, response to therapy, and survival in 263 adult patients with acute nonlymphoblastic leukemia. Blood 1980; 56:773-81.
11. Armitage O, Dick FR, Needleman SW, et al. Effect of chemotherapy for the dysmyelopoietic syndrome. Cancer Treat Rep 1981; 65:601-5.
12. Le Beau MM, Albain KS, Larson RA, et al. Clinical and cytogenetic correlations in 63 patients with therapy-related myelodysplastic syndromes and acute non-lymphocytic leukemia: further evidence for characteristic abnormalities of chromosomes no. 5 and 7. J Clin Oncol 1986; 4:325-45.
13. Tricot G, Boogaerts MA. The role of aggressive chemotherapy in the treatment of the myelodysplastic syndromes. Br J Haematol 1986; 63:477-83.
14. Fenaux P, Morel P, Rose C, et al. Prognostic factors in adult de novo myelodysplastic syndromes treated by intensive chemotherapy. Br J Haematol 1991; 77:497-501.
15. Kantarjian HM, Keating MJ, Walters RS, et al. Therapy-related leukemia and myelodysplastic syndrome: clinical, cytogenetic and prognostic features. J Clin Oncol 1986; 4:1748-57.
16. Lepelley P, Soenen V, Preudhomme C, Lai JL, Cosson A, Fenaux P. Expression of the multidrug resistance P-glycoprotein and its relationship to hematological characteristics and response to treatment in myelodysplastic syndromes. Leukemia 1994; 8:998-1004.
17. Estey E, Pierce S, Kantarjian H, et al. Treatment of myelodysplastic syndromes with AML-type chemotherapy. Leuk Lymphoma 1993; 11 (suppl 2):59-63.
18. Economopoulos T, Papageorgiou E, Stathakis N, et al. Treatment of high risk myelodysplastic syndromes with idarubicin and cytosine arabinoside supported by granulocyte-macrophage colony-stimulating factor (GM-CSF). Leuk Res 1996; 20:385-90.
19. Ruutu T, Hänninen A, Järventie G, et al. Intensive chemotherapy of poor prognosis myelodysplastic syndromes (MDS) and acute myeloid leukemia following MDS with idarubicin and cytarabine. Leuk Res 1997; 21:133-8.
20. Locatelli F, Zecca M, Pession A, Maserati E, De Stefano P, Severi F. Myelodysplastic syndromes: the pediatric point of view. Haematologica 1995; 80:268-79.
21. Lambertenghi Deliliers G, Annaloro C, Della Volpe A, et al. Single-institution results of autologous bone marrow transplantation in acute myeloid leukemia. Haematologica 1995; 80:136-41.