original paper
Haematologica 1997; 82:577-580

THE VALUE OF COMBINATION THERAPY IN ADULT ACUTE MYELOID LEUKEMIA WITH CENTRAL NERVOUS SYSTEM INVOLVEMENT

CARLO CASTAGNOLA, ANDREA NOZZA, ALESSANDRO CORSO, CARLO BERNASCONI
Divisione di Ematologia, IRCCS Policlinico San Matteo di Pavia, Istituto di Ematologia, Università degli Studi di Pavia, Italy

ABSTRACT

Background and Objective. In adult patients with acute myeloid leukemia (AML), central nervous system (CNS) involvement is a rare event and treatment has not yet been defined. Because there are no definitive data as to the most appropriate therapeutic approach to CNS leukemia in AML, we retrospectively analyzed a cohort of AML patients with meningeal leukemia in order to increase our knowledge on this particular matter.

Methods. Out of 410 patients with *de novo* AML observed at our Institute from 1986 to 1995, 9 (2.2%) showed CNS leukemia (CNSL) during the follow-up. CNSL was treated as follows: in a first group of 4 patients we combined systemic HD Ara-C 3 g/m^2 (every 12 hours by 3-hour infusion, for 6 doses), cranial radiation therapy and intrathecal (IT) methotrexate (MTX); a second group of 4 patients was treated with HD Ara-C, IT MTX without cranial irradiation; HD Ara-C alone was administered in one patient.

Results. All patients of the first group and 2 patients of the second who achieved a complete remission (CR) had a median survival of 10 months (range 5-25+) after CNS involvement, while for the non-remitters it was 2 months (range 1-5). The only patient still living underwent allogeneic bone marrow transplantation.

Interpretation and Conclusions. The combination treatment of HD Ara-C, IT MTX and cranial irradiation is well tolerated and seems to be an effective therapy for CNSL, presenting a high incidence of neurologic CR that correlates with a longer survival. As expected, the number of AML patients with CNSL was small, due to the fact that CNS in those patients is a rare complication. However, this study provides further information about the therapeutic possibilities in such restricted subsets of AML patients.

Key words: acute myeloid leukemia, CNS involvement, radio-chemotherapy

Central nervous system involvement is a well-recognized complication of acute lymphocytic leukemia (ALL) ranging between 20 and 40% of cases, and its prophylaxis has greatly reduced the incidence of CNSL as primary site of recurrence in adults.[1-3] On the contrary, due to the low frequency of CNS involvement in AML (2-4%)[4-6] prophylactic therapy is still controversial, although an overt meningeal leukemia, especially with concurrent systemic disease, still represents a major therapeutic problem.

Conventional treatment of CNSL consists of intrathecal (IT) chemotherapy with methotrexate (MTX) and/or cytarabine (Ara-C) plus meningeal irradiation.[7] Although this approach is usually effective in clearing cerebrospinal fluid, the remissions are usually short-lived.[8] Furthermore, CNS involvement is often followed by bone marrow (BM)[1] recurrence, which is consistent with the hypothesis that CNS represents a sanctuary for leukemia blasts that eventually repopulate the BM.[9] Therefore, a systemic chemotherapy appears more appropriate in treating CNSL both in ALL or AML; in particular, systemic high dose Ara-C (HD Ara-C) can be used alone or in combination with other therapeutic approaches. In fact, systemic HD Ara-C, which is active in resistant acute leukemia and non-Hodgkin's lymphoma, crosses the blood brain barrier achieving significant levels in the cerebral spinal fluid (CSF), thus permitting a more uniform distribution of the drug throughout the neuraxis.[10] In addition, due to the low levels of cytidine deaminase in the CNS, Ara-C catabolism in the CSF is lower than in the peripheral blood, which results in prolonged therapeutic levels of the drug.[11,12] On the basis of these observations, we used HD Ara-C in association with IT MTX with or without cranial irradiation, to treat 9 adult patients with AML and CNS involvement. We report herein the results of this combined approach.

Patients and Methods

From January 1986 to December 1995, 410 adult patients (172 men; 238 women) with recently diagnosed AML were admitted to our Institute.

Correspondence: Dr. Carlo Castagnola, Divisione di Ematologia, IRCCS Policlinico S. Matteo, piazzale Golgi, 27100 Pavia, Italy. Tel. international +39.382.503073 or 503070. Fax. international +39.382.502250.
Received May 8, 1997; accepted August 11, 1997.

The diagnosis was based on the morphological and cytochemical features of peripheral blood and bone marrow. According to the FAB classification criteria,[13] patients were defined as 21 M_0, 27 M_1, 111 M_2, 62 M_3, 134 M_4, 51 M_5, 4 M_6. CNS prophylaxis and spinal tap were not performed in any of the 390 patients (95%) who were eligible for receiving induction chemoterapy. Nine patients (2.2%), 8 men and 1 woman, developed a CNS involvement during the follow-up. They were classified as 2 M_2, 1 M_3, 4 M_4, 2 M_5 and the median age was 37 years (range 16-67). No patients had CNSL at the onset; 2 patients showed gum hypertrophy and 5 showed lymphoadenopathy, 3 of which had hepatosplenomegaly. The median WBC count was 52.7×10^9/L (range 5.5-223.0); blast cells were usually, but not invariably, present in the peripheral blood; abnormal eosinophils were detected in the marrow and peripheral blood of 3 patients (2 M_4, 1 M_5) and serum LDH ranged from 316 to 1143 U/L (Table 1). Induction chemotherapy included daunorubicin, standard dose Ara-c and etoposide in 8 patients; idarubicin was used as a single agent in the patient with M_3. Eight patients achieved hematological CR; 1 case was resistant to therapy. One patient underwent allogeneic BMT in early remission, but he experienced a BM relapse for which he received a further PBSC-transplantation from the same donor and achieved a second CR. CNS involvement was diagnosed in 5 patients with concurrent marrow relapse, in 3 patients in remission (2 of which subsequently relapsed at bone marrow), and in 1 patient who was primarily resistant.

Cytogenetic findings

Chromosome analysis was performed at diagnosis using Q-banding techniques and karyotype abnormalities were described according to the *International Society for Human Cytogenetic Nomenclature* criteria.[14]

In our series, chromosome analysis was performed in 6 patients and the cytogenetic abnormalities are listed in Table 2.

CNS involvement

CNSL, consisting of meningeal, nerve root or brain parenchymal involvement by leukemic blasts, is usually detected upon the cytological examination of CSF. No patients received CNS prophylaxis therapy. CNSL occurred after a median of 12 months (range 5-31) from diagnosis.

The main symptoms at diagnosis were headache or stiff neck, cranial or peripheral nerve palsy, mental derangement, papilloedema, nausea, vomiting, and vertigo. All patients had leptomeningeal disease with CSF pleocytosis, abnormal cytology, and a high protein level. The CSF blast count ranged from 78 to 2520/μL (median 350/μL). Abnormal eosinophils were detected in 1 patient's CSF.

Therapy of CNS leukemia

In a first group of 4 patients, we combined systemic HD Ara-C (3 g/m^2 every 12 hours, 3-hour infusion for 6 doses), cranial radiation therapy (24 Gy in 12 fractions) and IT MTX (15 mg for 4 doses); a second group of 4 patients was treated with HD Ara-C, and IT MTX without cranial irradiation; HD Ara-C alone was administered in one patient (Table 3).

Results

CNSL remission (defined as clearance of malignant cells from the CSF) was obtained in 6 patients (67%), including all patients treated with combined therapy (systemic HD Ara-C, IT MTX and radiation therapy) and the 2 treated with systemic HD Ara-C plus IT MTX. Three patients did not respond to treatment, and died due to CNSL. In one of these patients a thalamic myeloblastoma was demonstrated by CT scan and remained unchanged after

Table 1. Clinical and biological characteristics of 9 AML patients.

Pts	*Age (yrs)*	*Sex*	*FAB*	*Extramedullary disease at diagnosis*	*WBC (x 10^9/L)*	*LDH (U/L)*
PA	48	M	M2	nodes	17.8	874
NG	16	M	M4	nodes, spleen, liver	76.0	954
PA	39	F	M4	gum hypertrophy	223.0	789
MD	23	M	M3	spleen	35.2	316
PG	61	M	M4	nodes	38.7	1143
CA	27	M	M5	nodes, spleen, liver	51.3	490
SC	67	M	M2	nodes, spleen, liver	14.6	631
ZP	37	M	M5	—	11.7	456
TM	40	M	M4	gum hypertrophy	5.5	786

Table 2. Chromosome findings in relation to FAB classification.

Pts	*Chromosome findings*	*FAB*
TM	46xy, inv 16, +21 / 48xy, +21, +21 inv 16 / 46xy inv 16	M4
NG	46 xy /46 xy, inv 16	M4
ZP	46 xy	M5
PA	46 xy, t(8;21)	M2
PA	46 xx	M4
MD	46 xy / 46 xy, t(15;17)(q22;q11)	M3
SC	Failed	M2
NG	Failed	M4
CA	Failed	M5

Table 3. CR rates, CNS therapy and survival in relation to CNS involvement in 9 AML patients.

Pts	*Latency for CNS involvement from AML diagnosis (months)*	*Hematological status at time of CNSL diagnosis*	*CNSL therapy**	*CNSL CR*	*Hematological status at time of CNSL remission*	*CNSL relapse*	*Survival from CNSL (months)*	*Survival from AML diagnosis (months)*
PA	24	Relapse	HD-ara-C	No	NR	–	1	23,7
NG	29	Relapse	Schedule B	No	NR	–	5	33,6
PA	6	Relapse	Schedule B	Yes	RP	Yes	5	11,7
MD	11	Remission	Schedule A	Yes	RC	No	9	19,9
PG	12	Relapse	Schedule B	No	NR	–	2	14,3
CA	5	Remission	Schedule A	Yes	RC	No	12	16,9
SC	13	Refractory	Schedule B	Yes	NR	Yes	7	19,7
ZP	10	Relapse	Schedule A	Yes	RC	No	11	20,6
TM	31	Remission	Schedule A	Yes	RC	Yes	25	54,6 +

**Schedule A: Systemic HD-Ara-C 3 g/m² every 12 hours (3 hours infusion) for 6 doses, cranial radiation, intrathecal methotrexate.*
Schedule B: Systemic HD-Ara-C 3 g/m² every 12 hours (3 hours infusion) for 6 doses, intrathecal methotrexate

therapy. Of the 6 patients who entered CNSL complete remission, 3 had a meningeal relapse at 3, 6, and 20 months after CNSL remission. The patient that received allo-BMT is still living at 25 months after CNSL; he is in BM remission but displays persisting meningeal involvement (Table 3).

Discussion

Central nervous system involvement is quite uncommon in patients with AML, but it still represents a major therapeutic problem, whether it occurs during hematological relapse or remission.[7,15] Some studies performed on AML patients with CNSL showed that certain hematological parameters at diagnosis are related to an increased risk of CNSL: high WBC count, peripheral eosinophilia, high LDH levels, FAB sub-group (M_4-M_5), extra-hematological disease at presentation, male sex, and age < 50.[1,5] To date, no specific cytogenetic abnormalities have been associated with CNSL, except for chromosome 16 involvement.[5,10,16] In our patients, we confirm the presence of some of these features, in particular the FAB type M_4-M_5, the young age (7 out of 9 were under 50 yrs), male sex, and the involvement of chromosome 16 in only 2 patients (Tables 1 and 2).

CNSL therapy is still a controversial problem: conventional treatment of isolated CNSL with IT MTX and/or Ara-C associated with cranial irradiation[4,17] shows poor results because of the risk of marrow relapse.[7,9,18] Therefore, a systemic chemotherapy is necessary to prevent marrow reseeding in isolated CNSL, or to treat marrow involvement. Since chemotherapy with HD Ara-C had proven effective in acute leukemia and lymphoma,[15] and

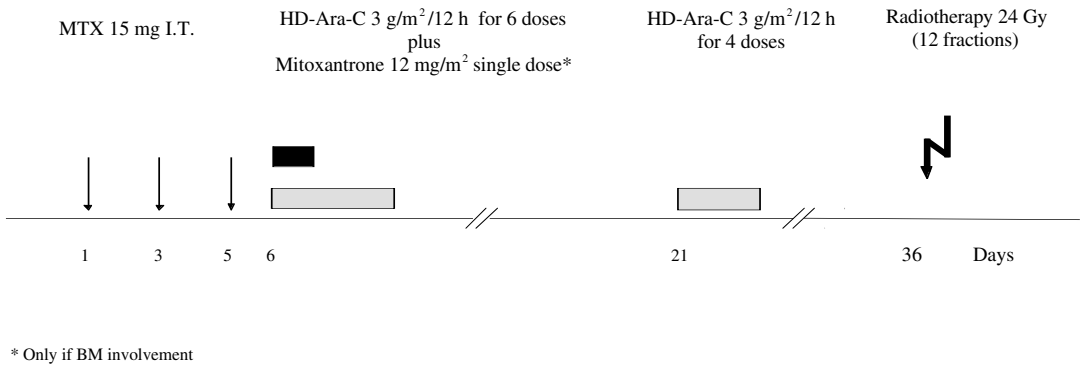

Figure 1. Operative guidelines for CNS leukemia in AML patients.

had achieved a high degree of penetration into CSF due to the low levels of the inactivating enzyme cytidine deaminase in CNS, it seemed worthwhile to add this drug to the CNSL therapy protocol.[19-21] However, the dose of Ara-C is crucial. Van Prooijen *et al*.,[22] using 500 mg/m^2 every 12 hours by 1 hour infusion for 6 days in patients with AML in relapse, observed a persistence of blasts in the CSF in 2 of 3 patients with concurrent meningeal leukemia. On the contrary, systemic infusion of the HD Ara-C (3 g/m^2) proved capable of establishing and maintaining potentially cytotoxic concentrations of the drug (over 0.2 (μmol/L) in the CSF for the entire duration of chemotherapy.[23,24] Therefore, it has been shown to be an effective therapy for CNS leukemia, mostly in cases with isolated CNS involvement.[11,12] Consequently, we used such doses to guarantee prolonged therapeutic levels of Ara-C in the CSF and brain tissue. This dosage, in combination with IT MTX and cranial radiation therapy, enabled us to obtain complete neurologic remission in 6 of 9 AML patients with meningeal leukemia; the median CR duration was 9 months with a range of 5-25+. One patient is still living, having received allogeneic bone marrow transplantation as consolidation therapy, but shows persisting meningeal involvement. On the contrary, the 3 non-remitters had a more serious prognosis.

In conclusion, our results indicate that the combination treatment (HD-Ara-C, IT MTX and cranial radiation therapy) is able to determine a high incidence of neurologic CR that correlates with a longer survival of this group of patients. Based on these findings, our operative guidelines for treatment of CNS involvement in AML are shown in Figure 1.

References

1. Stewart DJ, Keating MJ, McCredie KB, et al. Natural history of central nervous system acute leukemia in adults. Cancer 1981; 47:184-96.
2. Kantarjian HM, Walters RS, Smith TL, et al. Identification of risk groups for development of central nervous system leukemia in adults with acute lymphocytic leukemia. Blood 1988; 72:1784-9.
3. Livraghi A, Pagnucco G, Santagostino A, et al. Risk of central nervous system (CNS) involvement in adult acute lymphoblastic leukemia (ALL). Analysis of 168 cases [abstract]. Haematologica 1996; 81:34.
4. Rees JKH, Gray RG, Swirsky D, Hayhoe FGJ. Principal results of the medical research council's 8th acute myeloid leukemia trial. Lancet 1986; 29:1236-41.
5. Holmes R, Keating MJ, Cork A, et al. A unique pattern of central nervous system leukemia in acute myelomonocytic leukemia associated with inv (16)(p13q22). Blood 1985; 65:1071-8.
6. Bassan R, Barbui T. Remission induction therapy for adults with acute myelogenous leukemia: towards the ICE age? Haematologica 1995; 80:82-90.
7. Steinherz P, Jereb B, Galicich J. Therapy of CNS leukemia with intraventricular chemotherapy and low-dose neuraxis radiotherapy. J Clin Oncol 1985; 3:1217-26.
8. Stewart DJ, Smith TL, Keating MJ. Remission from central nervous system involvement in adults with acute leukemia. Cancer 1985; 56: 632-41.
9. Simone JV. Treatment of meningeal leukemia. J Clin Oncol 1984; 2: 357-8.
10. Ghaddar HM, Plunkett W, Kantarjian HM. Long-term followig treatment of newly-diagnosed acute myelogenous leukemia with continous-infusion high-dose cytosine arabinoside. Leukemia 1994; 8: 1269-74.
11. Morra E, Lazzarino M, Brusamolino E, et al. The role of systemic High-dose cytarabine in the treatment of central nervous system leukemia. Cancer 1993; 72:439-45.
12. Morra E, Lazzarino M, Brusamolino E, et al. High dose Ara-c for the treatment of CNS disease in adult acute lymphoblastic leukemia. New Trends Ther Leuk Lymph 1986; 1:1-7.
13. Bennet JM, Catovsky D, Daniel MT, et al. Proposal for the classification of the acute leukemias: French-American-British (FAB) cooperative group. Br J Haematol 1976; 33:451.
14. Third International Workshop on chromosome in leukemia. Cancer Genet Cytogenet 1980; 4:95-142.
15. Morra E, Lazzarino M, Inverardi D, et al. Systemic high-dose ara-C for the treatment of meningeal leukemia in acute lymphoblastic leukemia and non-Hodgkin' s lymphoma. J Clin Oncol 1986; 4: 1207-11.
16. Plantier I, Lai L, Wattel E, et al. Inv(16) may be one of the only favorable factors in acute myeloid leukemia: a report on 19 cases with prolonged follow-up. Leuk Res 1994; 18:885-8.
17. Bleyer WA, Poplack DG. Prophylaxis and treatment of leukemia in the central nervous system and other sanctuaries. Semin Oncol 1985; 12:131-48.
18. George SL, Ochs JJ, Mauer AM, et al. The importance of an isolated central nervous system relapse in children with acute lymphoblastic leukemia. J Clin Oncol 1985; 3:776-81.
19. Anonymous. Towards an increasingly molecular-based, patient-oreinted treatment of acute myeloiud leukemia [editorial]. Haematologica 1996; 81:1.
20. Rudnick SA, Cadman EC, Capizzi RL et al. High-dose cytosine arabinoside (HDaraC) in refractory acute leukemia. Cancer 1979; 44: 1189-93.
21. Capizzi RL, Yang JL, Cheng E, et al. Alteration of the pharmacokinetics of high-dose ara-C by its metabolite, high ara-U in patients with acute leukemia. J Clin Oncol 1983; 1:763-71.
22. Van Proijen HC, Dekker AV, Punt K. The use of intermediate dose cytosine arabinoside (ID ara-C) in the treatment of acute non-lymphocytic leukemia in relapse. Br J Haematol 1983; 57:291-9.
23. Van Proijen HC, Muus P, Reolofs JMP, et al. Does the metabolite uracilarabinoside inhibit cytosine arabinoside (ara-C) penetration into the cerebrospinal fluid during high-dose ara-C therapy? Scand J Haematol 1986; 36:123-6.
24. Chabner BA. Cytosine arabinoside. In: Chabner BA, Collins JM, eds. Cancer chemotherapy: principles and practice. Philadelphia: JB Lippincott; 1990. p. 154-79.