Cancer Chemother Pharmacol (1989) 25: 223–225

Cancer Chemotherapy and Pharmacology

Short communication

Phase II trial of plicamycin and hydroxyurea in acute myelogenous leukemia

Eric Archimbaud, Jacques Troncy, Catherine Sebban, Denis Guyotat, Yves Devaux, Martine French, Michel Moriceau[1], Jean-Jacques Viala, and Denis Fiere

Service d'Hématologie, Hôpital Edouard Herriot, Université Claude-Bernard, UER Alexis Carrel, Lyon, France
[1]Centre Médical Spécialisé, Praz-Coutant, France

Summary. A total of 23 patients with high-risk acute myelogenous leukemia (AML) at diagnosis (2 patients), relapsing AML (14) or resistant AML (6) were treated with 25 μg/kg i. v. plicamycin every other day for 3 weeks and 500 – 4,000 mg hydroxyurea per day p. o. according to the WBC count. Aplasia was observed in only two patients. Severe extrahematologic toxicity included sepsis (four cases), vomiting (four patients), toxic hepatitis (three cases), and fibrinopenia (one patient). No partial or complete responses were observed. The 95% confidence interval limit of the overall response rate (CR + PR) was 0 – 14%.

Introduction

Plicamycin (mithramycin), an inhibitor of RNA synthesis [15] initially used in the treatment of testicular cancer and malignant hypercalcemia, has recently been shown to induce differentiation of the HL-60 human promyelocytic leukemia cell line in vitro [12]. Hydroxyurea, an inhibitor of de novo synthesis of deoxynucleotides [10], has long been considered to be a very potent agent for the control of myeloid leukemic proliferations [8] and is a weak inducer of the differentiation of the HL-60 cell line in vitro [3]. Plicamycin and hydroxyurea have a synergistic effect in vitro on the differentiation of Friend murine erythroleukemia cells [4].

In a recent report, Koller and Miller [9] described the efficacy and low toxicity of plicamycin given every 2 days in association with daily hydroxyurea in reverting chronic myeloid leukemia (CML) in blastic crisis to the chronic phase, possibly by in vivo differentiation of blast cells, as marrow aplasia was not observed. This prompted us to initiate a phase II study of the regimen described by these authors in acute myelogenous leukemia (AML).

Patients and methods

Patients. Patients eligible for this study included those with a diagnosis of primary AML or AML following a myelodysplastic syndrome according to criteria of the Franco-American-British (FAB) Cooperative Group [1]. Patients were in either first (patients aged ⩾60 years) or subsequent relapse or were resistant to one (patients aged ⩾60 years) or two courses of conventional chemotherapy using anthracyclines and cytarabine. Elderly patients could also be entered at diagnosis when they refused conventional chemotherapy. Eligible patients were required to have a performance status of ⩽2 according to the WHO

Table 1. Initial characteristics in our 23 patients

Age (years)	[a] 66 (46 – 82)
Disease status:	
First diagnosis	2
Resistant	7
Relapsed[b]	14
Hemoglobin (g/l)	110 (77–142)
Platelet count ($\times 10^9$/l)	57 (4–160)
WBC count ($\times 10^9$/l)	3.7 (0.4–150)
Peripheral blasts (%)	30 (0–92)
Marrow blasts (%)	60 (15–95)
FAB subtype:	
M1	3
M2	7
M3	0
M4	6
M5	5
M6	1
Unclassified	1

[a]Median (range)
[b]Including 11 patients in first relapse and 3 in second relapse, with a median duration of previous CR of 6 months (range, 1–32 months)

Table 2. Extrahematologic toxicity according to the WHO grading system

Toxicity	WHO grade:			
	0	1–2	3–4	5
Infectious	17	2	3	1
Gastrointestinal	18	1	4	0
Hepatic	13	7	3	0
Hypocalcemia	21	2	0	0
Blood coagulation	22	0	1	0
Kidney	18	5	0	0

Offprint requests to: Eric Archimbaud, Service d'Hématologie, Hôpital Edouard Herriot, F-69437 Lyon Cedex 08, France.

scale [14] and to be free of hepatic, renal or blood coagulation defects.

A total of 23 patients entered this study; all gave informed consent according to our institutional policies. Their disease status, age and hematologic characteristics at the time of initiation of chemotherapy are shown in Table 1.

Chemotherapy regimen. The chemotherapy regimen used was similar to that described by Koller and Miller [9] except that hydroxyurea was given to all patients regardless of their initial WBC count to take advantage of a potential synergistic effect of this agent with plicamycin. Briefly, plicamycin was given i. v. at a dose of 25 μg/kg as a 3-h infusion every other day for 3 weeks, and hydroxyurea was given p. o. over the same period at a daily dose of 500 mg if the WBC count was $\leq 15 \times 109/l$ and at doses of 1,000, 1,500, 2,000, 3,000 or 4,000 mg when the WBC count was >15, >30, >50, >75, or $>100 \times 10^9/l$, respectively.

Blood counts, blood coagulation tests, creatininemia, calcemia and serum liver-enzyme levels were monitored before each administration of plicamycin. Prophylactic platelet transfusions were carried out to keep the platelet count above $20 \times 10^9/l$. All patients were given daily oral calcium during therapy to prevent plicamycin-induced hypocalcemia.

Analysis of results. Bone marrow smears were obtained both before and 3–6 days after the end of chemotherapy. Complete remission (CR), partial remission (PR) and failures were defined according to the Cancer and Leukemia Group B criteria [5]. Disease was considered to be progressive under therapy when the absolute blood blast cell count and/or bone marrow blast cell percentage increased by more than 50% during treatment. By comparison with results of a previous study using low-dose cytarabine, another putatively differentiating agent that results in responses (CR + PR) of at least 20% in advanced AML [2], we initially decided to close the protocol if no responses were observed in the first 19 patients evaluable for efficacy, corresponding to a CR percentage of $<15\%$, with a rejection error of 5% [6].

Results

The hematologic toxicity of this regimen was moderate, and only two patients developed aplasia or showed an exacerbation of preexisting pancytopenia. The extrahematologic toxicity is shown in Table 2. Toxicities of grade 3 or more included sepsis (four patients, including one death during aplasia), severe vomiting (four cases), toxic hepatitis (three patients) and possibly plicamycin-related fibrinopenia (one case). Overall, therapy was interrupted due to toxicity in two patients and due to an intercurrent cerebral arterial thrombosis in one case with a past history of thrombosis. Therapy could be carried out on an outpatient basis in 15 patients, whereas 8 had to be hospitalised at various times during the course of treatment.

None of the patients achieved a CR or PR. Overall, there was evident progression of disease under therapy in 12 patients, whereas the disease remained stable in 11 cases. The 95% confidence interval limit for the percentage of responses (CR + PR) in the 23 patients was 0–14%.

Discussion

The efficacy of plicamycin and hydroxyurea in CML in blastic crisis, initially noted by Koller and Miller [9], has been controversial in several subsequent studies [13]. This regimen failed to induce a response in two cases of Ph^1-positive acute leukemia but possibly reduced transfusional needs in one patient with myelodysplastic syndrome in transformation to acute leukemia [7].

The lack of response observed in our 23 AML patients treated with plicamycin and hydroxyurea indicates that this regimen is probably not useful for the treatment of AML. However, no patient with FAB M3 AML, the only FAB subtype in which the in vivo efficacy of differentiating agents such as retinoids has been demonstrated [11], was treated in the present study. A limited study of this regimen in relapsed FAB M3 AML might therefore be necessary before the possible activity of plicamycin and hydroxyurea in inducing in vivo differentiation of AML cells can be ruled out.

References

1. Bennett JM, Catovsky D, Daniel MT, Flandrin G, Galton DAG, Gralnick HR, Sultan C (1985) Proposed revised criteria for the classification of acute myeloid leukemia: a report of the French-American-British Cooperative Group. Ann Intern Med 103: 626
2. Bolwell BJ, Cassileth PA, Gale RP (1987) Low dose cytosine arabinoside in myelodysplasia and acute myelogenous leukemia: a review. Leukemia 1: 575
3. Collins SJ, Bodner A, Ting R, Gallo RC (1980) Induction of morphological and functional differentiation of human promyelocytic leukemia cells (HL-60) by compounds which induce differentiation of murine leukemia cells. Int J Cancer 25: 213
4. Eberts PS, Wars I, Buell DN (1976) Erythroid differentiation in cultured Friend leukemia cells treated with metabolic inhibitors. Cancer Res 36: 1809
5. Ellison RR, Holland JF, Weil M, Jacquillat C, Boiron M, Bernard J, Sawitsky A, Rosner F, Gussoff B, Silver RT, Karanas A, Cuttner J, Spurr CL, Hayes DM, Bloom J, Leone LA, Haurani F, Kyle R, Hutchison JL, Forcier RJ, Moon JH (1968) Arabinosyl cytosine: a useful agent in the treatment of acute leukemia in adults. Blood 32: 507
6. Gehan EA (1961) The determination of the number of patients required in a preliminary and follow-up trial of a new chemotherapeutic agent. J Chronic Dis 13: 346
7. Hassan A, Raza A, Mandava N, Baer MR, Stein A, Preisler HD (1987) Efficacy of mithramycin and hydroxyurea in blastic crisis of CML, Ph^1 positive acute leukemia and myelodysplasia. Blood 70 [Suppl 1]: 230 a
8. Koeffler HP (1981) Chronic myelogenous leukemia: new concepts. N Engl J Med 304: 1201
9. Koller CA, Miller DM (1986) Preliminary observations on the therapy of the myeloid blast phase of chronic granulocytic leukemia with plicamycin and hydroxyurea. N Engl J Med 315: 1433
10. Krakoff IH, Brown NC, Reichard T (1968) Inhibition of ribonucleoside diphosphate reductase by hydroxyurea. Cancer Res 28: 1559
11. Meng-er H, Yu-Chen Y, Shu-rong C, Jin-ren C, Jia-Xiang L, Lin Z, Long-jun G, Zhen-yi W (1988) Use of all-trans retinoic acid in the treatment of acute promyelocytic leukemia. Leukemia 72: 567
12. Polansky DA, Koller CA, Miller DM (1983) Inhibition of RNA synthesis induces differentiation of promyelocytic leukemia cells. Blood 62 [Suppl 1]: 153 a

13. Trümper LH, Ho AD, Hunstein W, Lelie H van der, Goudsmit R (1989) Therapy of the myeloid blast phase of chronic granulocytic leukemia with plicamycin and hydroxyurea. Blut 58: 85
14. World Health Organization (1979) Handbook for reporting results of cancer treatment. WHO offset publication 48. WHO, Geneva
15. Yarbro JW, Kennedy BJ, Barnum CP (1968) Mithramycin inhibition of ribunocleic acid synthesis. Cancer Res 26: 36

Received 23 May 1989/Accepted 15 July 1989