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Acral Erythema and Systemic Toxicity Related to CHA Induction Therapy in Acute Myeloid Leukemia

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Abstract—*Seventy-two adult patients with previously untreated acute myeloid leukemia received the CHA regimen as induction chemotherapy: CCNU* 80 mg/m² *on day* 1, *Adriamycin®* 35 mg/m² *i.v. on days* 1, 2 *and* 3, *and continuous infusion of cytarabine* 100 mg/m²/24 h *from day* 1 *to* 10. *Forty-nine patients* (68%) *presented at least one of the following symptoms: acral erythema with dysesthesias in the palms and/or soles* (39%); *cholestatic hepatitis* (39%); *profuse sterile diarrhea associated with abdominal distention* (33%); *acute cerebellar dysfunction* (32%) *and non-cardiogenic pulmonary edema* (21%). *Most of these toxic symptoms appeared* 8–20 *days after the first dose. As these clinical features were absent or exceptional in patients treated with another regimen within a controlled trial, they are reported as toxic side-effects of the chemotherapy regimen.*

Acral erythema was found to be predictive of complete remission ($P < 0.01$, *odds ratio*: 6.33); *neurotoxicity was prognostic for death in aplasia* ($P < 0.05$); *the absence of any of the five symptoms was associated with failure of the induction regimen* ($P < 0.02$).

INTRODUCTION

As soon as intensive chemotherapies permitted induction of complete remission in acute myeloid leukemia, physicians were confronted with their side-effects. Although 60–80% of patients achieve remission after intensive induction therapy, controversy still remains regarding optimal treatment for long-term disease-free survival [1–3]. In an attempt to improve these results, two induction regimens, CHA and VRAC, were compared in a randomized prospective controlled trial. The CHA association emerged as more effective than the VRAC [4, 5]. However, several unusual clinical symptoms occurred in the induction phase of the treatment.

The aim of the present study was to characterize and describe these symptoms, to clarify the responsibility of the induction regimens, to look for possible associations between these features and to evalute their prognostic value either on immediate evolution or on 1-year survival.

PATIENTS AND METHODS

Patients

Between 1 January 1978 and 1 January 1982, 93 patients with acute myeloid leukemia (AML), aged 15–70 years, were included in a prospective controlled trial. Patients with acute promyelocytic leukemia were excluded. After randomization 50 patients received CHA and 43 VRAC. From 1 January 1982 to October 1985, 25 new patients were included in an open study with the CHA induction treatment.

The composition of the two treatments, CHA and VRAC, is described in Table 1. Each group received the same supportive care. All patients were treated in private rooms with reverse protective isolation. Erythrocyte transfusions were administered to maintain the hematocrit level above 30%. Platelet

Table 1. *CHA and VRAC: drug composition of induction chemotherapy*

Drugs (mg/m²/day)		Route	Days
VRAC			
Vincristine	1	i.v.	1
Rubidazone	200	i.v.	2,3,4
CCNU	40	per os	5,6
Aracytine	100	continuous i.v. infusion	2–6
CHA			
CCNU	80	per os	1
Doxorubicin	35	i.v.	1,2,3
Aracytine	100	continuous i.v. infusion	1–10

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transfusions were also administered to maintain the platelet count above 30×10^9/l. Furthermore, patients received daily prophylactic granulocyte transfusions (mean dose 1.6×10^{10} leucocytes/m^2/day). Oral non-absorbable antibiotics were given to every patient. In a case of fever, a pre-established parenteral combination of antibiotics was used.

Statistical methods

Comparisons of qualitative data were made by the chi-square method. Comparisons of means of quantitative data were made using analysis of variance. Prognostic symptoms of first complete remission, or of 1-year survival, were looked for using an ascendant stepwise logistic regression model [6].

RESULTS

Possible side-effects of the two induction chemotherapies were evaluated in 90 patients who entered the prospective controlled trial and in 25 patients who were consequently integrated in an open study with the CHA treatment only. Three patients for whom necessary information could not be gathered were not retained in the analysis.

The pre-treatment clinical and hematological characteristics of the patients were not different in the two treatment groups (Table 2).

Description of the clinical and/or biochemical symptoms

An unusual occurrence of five clinical and/or biochemical symptoms was observed in the first days following the end of induction. They were invariably associated with fever and were characterized by their clinical presentation.

Acral erythema. Dysesthesias in palms and/or soles took place, then pain developed, associated with swelling and erythema. Over the next few days, the lesions evolved with blanching between joints and dusky red bands about articulations appeared. The blanched zones became bullous. Over the following week, hands and/or feet underwent desquamation. These peculiar lesions were always symmetrical and sterile.

This description corresponded to the more complete clinical presentation since more discrete forms were also observed. Pathological findings ($n = 9$) were non-specific and usually showed mild infiltration of superficial dermis with mononuclear cells. Bullous formations were noted in two cases and mild vasculitis of small vessels in two others. Immunofluorescence studies were negative in 3/3 patients.

Diarrhea and abdominal distension. Association of profuse sterile diarrhea with abdominal distension.

Central nervous system involvement. Central nervous system (CNS) involvement associated with various degree of impairment: cerebellar dysfunction characterized by dysarthria, dysdiadochokinesia, ataxia and/or tremor, and cerebral cognitive dysfunction with personality changes and/or somnolence.

Pulmonary edema. Acute respiratory distress syndrome related to non-cardiogenic edema without evidence of uncontrolled sepsis.

Cholestatic hepatitis. Rise of alkaline phosphatase and serum aspartate amino transferase over twice upper normal limit.

Prevalence of the signs in the CHA induction treatment

The prevalence of the five clinical symptoms was markedly different in the two groups of treatment. The five signs were more prevalent in the CHA group. Three of them were only present in the CHA group: neurologic symptoms ($n = 14$; $P < 0.001$), diarrhea with abdominal distension ($n = 14$; $P < 0.001$) and acral erythema ($n = 9$; $P < 0.01$). A non-cardiogenic pulmonary edema was present in nine patients of the CHA group and in only one patient of the VRAC group ($P < 0.01$). Eleven cases of cholestatic hepatitis were noted in the CHA

Table 2. Patient population

	Controlled trial		Open trial
Regimen	VRAC	CHA	CHA
Number of patients	43	47	25
Sex (M/F)	25/18	27/20	10/15
Age (years)	38.4 ± 7.3	34.6 ± 7.2	38.8 ± 5.4
Leucocytes ($\times 10^9$/l)	35.8 ± 32.5	58 ± 41.4	66.8 ± 36.5
FAB*			
1	14	12	3
2	16	15	5
4	8	14	11
5	4	5	6
6	1	1	0

*FAB = French–American–British cytological classification.

Table 3. Toxicity of the CHA regimen (72 patients)

	Number of patients	Delay to onset (days) Mean ± S.D.	Range
Acral erythema	28 (39%)	10.1 ± 1.3	8–12
Cholestatic hepatitis	28 (39%)	12.1 ± 4.4	2–23
Diarrhea	24 (33%)	12.4 ± 3.1	7–18
CNS toxicity	23 (32%)	13.1 ± 4.3	3–20
Pulmonary edema	15 (21%)	13.1 ± 2.9	8–20

Table 4. Prognostic value of the toxic symptoms. Results of CHA induction

	Complete remission	Failure	Death in aplasia
Acral erythema	25*	2	1
Cholestatic hepatitis	21	3	4
Diarrhea	17	3	4
CNS toxicity	15	2	6**
Pulmonary edema	11	1	3
None of the symptoms	13	8***	2
1 symptom	12	3	1
2 symptoms	8	0	2
3 symptoms	7	1	3
4 symptoms	8	0	1
5 symptoms	2	1	0
All patients (n = 72)	50	13	9

*$P < 0.01$; **$P < 0.05$; ***$P < 0.02$.

versus three in the VRAC group ($P < 0.02$). Thus, these signs were related to CHA.

In the CHA group, age, sex, leucocyte count, FAB classification or intercurrent septic episodes were not significant explanatory co-predictors of these side-effects. However, the mean (± S.D.) aplasia period, defined as the number of days with a granulocyte count below 1×10^9/l, was longer with the CHA regimen (26.6 ± 1.2 days) than with the VRAC regimen (19.1 ± 1.1 days). This was also true when the group of 25 patients treated in the open study was considered. This group was subsequently integrated in the following steps.

Symptomatic association and prognostic value of the signs

When present, these symptoms could be associated in the same patient. Only one sign was present in 16 patients, but two signs coexisted in 10 patients, three in 11, four in nine and five in three patients. The mean delay of onset was homogeneous. As the induction treatment lasted 10 days the clinical features occurred within the very first days following the end of induction therapy (Table 3).

Whether the side-effects were prognostic markers of complete remission following induction was evaluated using a logistic regression model.

The presence of acral erythema was predictive of complete remission with an odds ratio of 6.33. In other words, occurrence of complete remission was six times greater in patients who experienced acral erythema than in patients who did not.

Conversely, the presence of neurological symptoms was predictive of death in aplasia with an odds ratio of 4.81. Failure of induction chemotherapy to induce complete remission was statistically more frequent in patients with none of the toxic signs than in patients who experienced at least one of these signs (Table 4).

Attempt to treat the side-effects

Thirty-five of the 49 patients who presented at least one side-effect received corticosteroids. The mean daily dose of hydrocortisone was 220 mg (100–450 mg) for a mean duration of 11 days (2–17). Rapid resolution of the systemic signs was obtained in 19 patients (39%) and ineffectiveness was apparent in 10 patients. In the other cases the clearest non-specific effect of steroids was a decrease of fever.

DISCUSSION

Five unusual symptoms occurred with an unexpected prevalence in patients with acute myeloid leukemia treated in a prospective randomized trial comparing two induction regimens: CHA and VRAC. It was shown that these signs were signifi-

cantly related to the CHA induction therapy. CHA showed an association of high cumulative doses of cytarabine, CCNU and Adriamcyin®. The signs appeared just after the end of induction therapy that lasted for 10 days. They involved skin, digestive tract, central nervous system, lungs and liver. These systemic symptoms were respectively acral erythema, diarrhea with abdominal distension, cerebellar and/or cognitive dysfunctions, non-cardiogenic edema and cholestatic hepatitis.

The pathophysiology of these signs remained unclear. The possibility of a graft-versus-host disease was suggested by the association of cutaneous, hepatic and gastrointestinal involvement. However, the nature of the symptoms was clearly different. Furthermore, histological data were not consistent with this hypothesis. Finally, the symptoms even appeared in six of eight patients only transfused with irradiated blood products. A toxic hypothesis was more likely. These signs were suspected to be toxic manifestations of the peculiar association of drugs which constituted the CHA induction treatment. The chronology of occurrence within the very first days following the end of induction therapy, the nature of the symptoms and previous reports in the literature were compatible with this hypothesis.

Such symptoms had been reported as potential side-effects of chemotherapeutic agents. Thus acral erythema had been already described in one patient with acute myeloid leukemia treated by cytarabine, doxorubicin and vincristine sulfate [7] and in several patients receiving doxorubicin and continuous infusion of 5-fluorouracil for cancer [8]. Central nervous system involvement with acute cerebellar syndrome had been observed in patients treated with high dose of cytarabine or with 5-fluorouracil [9]. Most of the side-effects herein reported have already been noted with high-dose cytarabine. The most similar effect to our report concerns central nervous system involvement with acute cerebellar dysfunction. Neurotoxicity is dose-related and usually occurs in patients receiving a cumulative dose higher than 24 g/m^2 [9–11]. Damage caused to Purkinje cells might be related either to cytarabine itself by direct toxic effect or to its metabolites. They might have a prolonged cerebrospinal fluid half-life and increased concentrations [12, 13]. Other side-effects of high dose cytarabine involve the gastrointestinal tract, liver, skin, lungs and eyes [7, 14–18]. Using conventional doses of cytarabine with a total cumulative dose of 1 g/m^2, we observed all these side-effects but no conjunctivitis.

Several side-effects could be associated in the same patient. Thirty-three patients presented two to five associated signs, but acral erythema was not statistically associated to the other systemic symptoms.

These results might suggest either potentially different modes of toxicity of the drugs involved, or different personal susceptibility to this association of drugs. The specificity of the CHA schedule might be responsible for its unexpected toxicity, especially the continuous infusion procedure and the duration of treatment (10 days) [19]. However, a similar schedule, including 100 mg/m^2/24 h cytarabine infusions for 10 days associated with Adriamycin® 30 mg/m^2/day on days 1, 2 and 3, was not reported to be responsible for such toxicity [2]. Therefore, CCNU might contribute towards potentializing cytarabine-related toxicity. This potentialization was expected when toxicity towards blast cells was considered [20], since CHA appeared as the most efficient induction treatment.

Side-effects had a significant prognostic value regarding the issue of the induction regimen. Acral erythema was predictive for a more favorable outcome since patients who presented this sign had a six times greater chance of reaching complete remission than patients who did not. However, acral erythema was not predictive of 1-year disease-free survival. The absence of any of the five side-effects appeared significantly prognostic of failure of induction therapy. This confirmed the peculiar place of acral erythema which did not interact with the other systemic signs.

In conclusion, drugs associated in the CHA regimen were suspected to be the cause of frequent side-effects in this group. The clinical features suggest the responsibility of cytarabine but a complex interaction between the chemotherapeutic agents, intensive hematologic support and anti-infection prophylaxis is probably involved. The goal of the treatment was to be effective in blast cell destruction with minimal side-effects production. As far as CHA appeared as an interesting induction therapy of acute myeloid leukemia, bioequivalence assays would be required to establish the optimal doses of drugs to optimize the ratio between maximal survival rate and minimal side-effects.

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