Therapy of the Blast Phase of Chronic Granulocytic Leukemia with Mithramycin and Hydroxyurea¹

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Introduction Therapy

It is well known that the therapeutic strategies available so far for the blast phase of chronic granulocytic leukemia (CGL) are ineffective especially for the myeloid one. Recently a new treatment regimen was reported using the combination of alternate-day mithramycin and daily hydroxyurea suggesting a return to the chronic phase without an intervening pancytopenic period in all 6 patients with myeloid presentation whereas none of the 3 patients with lymphoid or undifferentiated blast crisis responded [1]. This observation would be of important clinical as well as theoretical interest because of the possible role of this regimen as a cell differentiation inducer. To confirm this preliminary observation further patients with blast phase of CGL were treated by this regimen at different German hematological centers.

All 15 patients were treated by the same regimen mentioned above [1]. Initially, mithramycin was given at a dose of 25 µg per kg of body weight in 0.25 to 0.51 of 5% glucose in water infused intravenously over a period of 2 to 4 h every other day for 3 weeks. Concurrent daily hydroxyurea was given orally depending on the total WBC count as follows: WBC more than 100,000/µl, 4g/day; more than 75,000/µl, 3g/day; more than 50,000/µl, 2g/day; more than 30,000/µl, 1.5g/day; more than 15,000/µl, 1 g/day; more than 7,500/µl, 0.5 g/day, and less than 7,500/µl, no hydroxyurea. If a patient responded to the initial 3-week trial, a maintenance regimen was instituted consisting of mithramycin infusions 1-3 times per week, as well as daily hydroxyurea according to the above schedule.

Material and Methods

Patients

Fifteen patients (male/female 9/6) entered the study, of whom 14 had CGL and 1 had osteomyelofibrosis. The mean age at initial diagnosis was 47 (18-74) years, the chronic phase of

the disease lasted 32 (4-117) months. During the stable chronic phase the patients received busulfan (8), hydroxyurea (1), both (4), busulfan and others (1) and none (1, OMF). From January 1986 to September 1987, the patients developed blast crisis. Cytologically the blasts showed myeloid differentiation in 14 and no differentiation in 1 patient. TdT was positive in 1/7 patients, myeloid antigens were found in 10/10 patients. Pretreatment (vincristine-glucocorticoid; mitoxantrone) was performed in 2/15 patients.

The mean hematological data at start of treatment with mithramycin and hydroxyurea were: hemoglobin 9.7 g% (7.3-13.5), platelets 116,000/ μ l (6000-594,000), WBC 42,200/ μ l (1,000-100,000), blasts 18,600/ μ l (0-71,000).

1 Initiated by the Süddeutsche Hämoblastosegruppe.

Results

The induction regimen of mithramycin and hydroxyurea for the period of 3 weeks could only be completed in 9/15 patients. The mean total dose of mithramycin in 10 patients was 18.2 mg and of hydroxyurea in 9 patients was 43.7 g. The cause of uncompleted induction was: no hydroxyurea (1), treatment duration only 2 weeks and less (5). The cause of treatment interruption was early death (3) and rapid worsening of personal condition (2). The maintenance treatment could only be performed in 1/15 patients (table I).

A complete or partial remission as expressed by the bone marrow cellularity could not be established in any of the patients. However, a reduction of the peripheral blast count of more than 50% was observed in 4/9 evaluable patients. The 4 patients survived 1, 1.25, 1.5 and 6 months from start of treatment. In another patient a stable disease for 3 months was reached. She obtained maintenance treatment for 6 weeks (mithramycin 31.5 mg; hydroxyurea 63 g) and died after 4 months from start of treatment. At the time of evaluation 3 patients were alive (+3 months +12 months, +20 months) and 12 have died. The mean survival of the 12 patients from the time of diagnosis was 2.9 months and from start of treatment 2.0 months (table I).

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Short Communication/Kurzmitteilung

Table I. Treatment results of 15 patients with terminal blast phase of chronic granulocytic leukemia after mithramycin and hydroxyurea

Induction

9/15 18.2 mg (14.4-24 mg) 43.7 g (19-63 g) 6/15

Mithramycin + hydroxyurea, 3 weeks Total dose of mithramycin (n = 10)

Total dose of hydroxyurea (n = 9)

Uncompleted treatment No hydroxyurea 1

Treatment for 2 weeks (early death) 4 Treatment for 1 week (early death) 1

Maintenance

1/15

Mithramycin + hydroxyurea

Response

Evaluable for response 9/15

Complete + partial remission

(bone marrow) 0/9

Reduction of peripheral blasts > 50 % 4/9

No change (3 months) 1/9

Progression (peripheral blasts) 5/9

Survival

Alive (+1 months, +10 months,

3/15 12/15

2.9 months (1-6 months) 2.0 months (0.25-6 months)
+ 11 months)

Dead

Mean survival diagnosis – death (n = 12)

Mean survival start of treatment -death (n=12)

Treatment was well tolerated in all 15 patients. Mithramycin did not lead either to a rise of the liver enzymes or to transient hypocalcemia at the dose level used. No toxic effects ascribed to hydroxyurea were found in this trial.

Comment and Conclusion

The median survival of patients with CGL who have entered the blast phase has continued to be 2-3 months and of those showing TdT-positive lymphoid blast phase 3-5 months [2, 3]. In the series of 6 patients with myeloid blast crisis treated by mithramycin and hydroxyurea the total duration of response

ranged from 5-19 months, the median duration of response being 8 months [1].

Concerning our series including 15 patients with blast phase (14 with myeloid differentiation) these recent data could not be confirmed. Five patients had early death despite of induction treatment. Within the 9 evaluable patients a reduction of peripheral blasts of more than 50% was seen in 4. However, complete or partial response of the bone marrow and reconstitution of chronic phase of the disease could not be observed in any of the patients. Consequently the survival did not exceed the 2-3 months which is reported for other treatment modalities.

Concerning the patient characteristics the mean age of our 15 patients (47 years) was similar to that reported of the 6 patients with myeloid blast phase (42 years) in the previous publication [1]. Two and 3 patients, respectively, were pre-treated with other agents. In most cases of both studies, treatment with mithramycin and hydroxyurea was started immediately after the diagnosis of blast crisis was established. Therefore a significant difference of the patient population explaining the different treatment results cannot be recognized.

In conclusion, in our opinion this treatment is not effective for myeloid blast phase of CGL, and the study group has resigned to institute a prospective phase-II-trial.

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