short report
Haematologica 1995; 80:532-534

CLONAZEPAM PROPHYLAXIS AND BUSULFAN-RELATED MYOCLONIC EPILEPSY IN AUTOGRAFTED ACUTE LEUKEMIA PATIENTS

Giovanna Meloni, Laura Nasta,* Rita Maria Pinto, Alberto Spalice,* Umberto Raucci,* Paola Iannetti*

*Hematology Division, Department of Biopathology and *Department of Pediatrics, Division of Child Neurology; University "La Sapienza", Rome, Italy*

ABSTRACT

A prospective neurological and electroencephalographic (EEG) study was performed in sixteen leukemia patients receiving busulfan (BU) and cyclophosphamide before autologous bone marrow transplantation. All patients were given anticonvulsant prophylaxis with a combination of phenobarbital (PB) and clonazepam (CLZ). Neurological examination and EEG were performed prior to and soon after completion of BU treatment and were repeated two months later. No tonic-clonic and/or myoclonic convulsions were observed. In two patients, comparison of EEG recorded before and upon completion of BU administration revealed modification of features. EEG re-evaluated two months after BU showed normalization in one of the two patients. BU may trigger both generalized and myoclonic seizures together with EEG abnormalities; PB combined with CLZ may be useful prophylactic treatment.

Key words: autografted acute leukemia, busulfan, barbiturate, clonazepam, neurological-EEG evaluation

©Ferrata Storti Foundation

The poor prognosis of acute myeloid leukemia (AML)[1] has lead to the use of autologous bone marrow transplantation (ABMT) as a means for intensification of post-induction chemotherapy. High-dose busulfan (BU) is employed in the myeloablative regimens for ABMT, and anticonvulsant prophylaxis is generally adopted to obviate seizures caused by these regimens.[2-5] Nevertheless, myoclonic epilepsy has been observed during anticonvulsant barbiturate and phenytoin prophylaxis.[5-8] Clonazepam (CLZ) has been used in children for the prevention of both tonic-clonic and myoclonic seizures.[9]

To clarify the role of CLZ, we carried out a neurological and electroencephalographic (EEG) study among sixteen AML patients submitted to the BU regimen and subsequent ABMT. All patients were administered a combination of phenobarbital (PB) and CLZ for prophylaxis of both tonic-clonic and myoclonic convulsions.

Materials and Methods

Sixteen consecutive patients with AML underwent ABMT (nine males and seven females, age span 13-58 years, median age 27 years); fifteen of them were in first complete remission (CR) and one in second CR. ABMT was performed a median of three months (range 1-6 months) after the latest CR. The patients had no clinical signs of central nervous system disease; five of them had previously undergone brain computed tomography or magnetic resonance imaging and all results were normal. The conditioning regimen used consisted of BU (4 mg/kg/day given orally over four consecutive days), followed by cyclophosphamide (CY) (60 mg/kg/day for the next two days); stem cell reinfusion was performed 48 hours after the last dose of CY. The patients underwent anticonvulsant prophylactic treatment with PB 100 mg once a day and CLZ 2.1 mg three times a day. CLZ administration was started three days before BU and was continued until stem cell reinfusion; PB was begun

Correspondence: Giovanna Meloni, M.D., Institute of Hematology, University "La Sapienza", via Benevento 6, 00161 Rome, Italy. Tel. international +39.6.857951; Fax international +39.6.85795293.
Received June 12, 1995; accepted August 4, 1995.

at the same time as CLZ and was tapered over the following 2 months.

Clinical and neurological examinations and EEGs were performed before and at the end of BU administration, prior to CY treatment and within two months after transplantation. Routine analyses were carried out in all the patients examined.

Results

No neurological abnormalities were observed. EEGs performed one week before BU administration were normal in ten of the sixteen patients; focal abnormalities were detected in two patients and generalized abnormalities in four others (Table 1). EEGs recorded at the end of BU and prior to CY administration showed continued normality in eight patients, no modifications of previous features in six and the appearance of abnormalities in two patients (focal in one and generalized in the other) (cases #2 and #14, respectively, in the table). EEGs re-evaluated in all patients one or two months later showed normal activity in the patient with focal abnormalities (patient #2) and no change in the remaining patients (Table 1). No myoclonic or tonic-clonic seizures were observed.

Table 1. Neurological and EEG evaluation in leukemia patients undergoing busulfan treatment for autologous bone marrow transplantation in prophylactic treatment with phenobarbital and clonazepam.

Pts	*Age/sex (yrs)*	*Disease status*	*EEG before 1 week*	*EEG after 8-10 h.*	*Neuro*	*EEG follow-up (within 2 mos)*
1	48/M	1	FA	FA	–	FA
2	45/F	1	N	FA	–	N
3	21/F	1	N	N	–	N
4	46/F	1	N	N	–	N
5	24/M	2	GA	GA	–	GA
6	13/F	1	GA	GA	–	GA
7	17/M	1	N	N	–	N
8	23/F	1	FA	FA	–	FA
9	18/M	1	N	N	–	N
10	33/M	1	N	N	–	N
11	41/F	1	GA	GA	–	GA
12	51/F	1	N	N	–	N
13	32/M	1	N	N	–	N
14	58/M	1	N	GA	–	GA
15	15/M	1	N	N	–	N
16	16/F	1	GA	GA	–	GA

Abbreviations: AML: acute myeloid leukemia; CR: complete remission; FA: focal abnormalities (slow and sharp waves; GA: generalized abnormalities (slow wave complexes and sharp waves; N: normal.

Discussion

High-dose BU used in the conditioning regimen for bone marrow transplantation (BMT) can trigger both tonic-clonic and myoclonic convulsions.[1-7] Since an increasing number of patients have been undergoing BMT with regimens including BU, anticonvulsant prophylaxis has become mandatory for the prevention of cerebral complications.[5]

Various anticonvulsant drugs have been used,[5-7] but none of them has succeeded in preventing myoclonic epilepsy. In a previous neurological and EEG study performed in leukemia patients undergoing high-dose BU therapy and PB prophylactic treatment, an overall incidence of myoclonus of 28% was found despite PB administration; when CLZ was added to PB myoclonus disappeared. Furthermore, myoclonus seemed to be age-related and dose-dependent and did not occur in young patients.[8] The drug's neurotoxicity seems to be related to its capacity to cross the blood-brain barrier rapidly after oral administration. Exposure of the brain to BU or its metabolites may result in myoclonus epilepsy. CLZ, a benzodiazepine with anticonvulsant activity, rapidly suppresses many types of generalized paroxismal activity.[10]

In our patients the oral prophylactic treatment with PB (100 mg/day) and CLZ (2.1 mg/day) seemed to be effective. No generalized tonic-clonic and/or myoclonic convulsions were observed in any of the patients examined. The EEGs performed one week before high-dose BU showed abnormalities in six of the fourteen patients probably related to previous treatment. During and after BU administration only two patients showed mild EEG abnormalities not related to neurological symptoms.

Anticonvulsant prophylaxis is recommended during high-dose BU. PB is considered useful for the prevention of generalized tonic-clonic

©Ferrata Storti Foundation

seizures, while CLZ should be used for myoclonic epilepsy control, beginning at least two or three days before the pretransplant conditioning and tapered gradually over the first 72-96 hours following the last dose of BU.

Our ultimate goal is to use only one drug and CLZ seems to be a good candidate for successful prevention of both generalized and focal motor seizures and myoclonic epilepsy in patients treated with BU.

Nevertheless, there is an obvious need for further studies on the role and usefulness of prophylactic anticonvulsant drugs during BU pretransplant conditioning.

References

1. Rigolin GM, Fagioli F, Spanedda R, et al. Study of prognosis in acute myeloid leukemias (AML) by cluster analysis. Haematologica 1994; 79: 233-40.
2. Marcus RE, Goldman JM. Convulsions due to high-dose busulphan. Lancet 1984; 2:1463.
3. Martell RW, Sher C, Jacobs P, Monteagudo F. High-dose busulfan and myoclonic epilepsy. Ann Intern Med 1987; 106:1073.
4. Sureda A, Perez de Oteyza J, Garcia Larana J, Odriozola J. High-dose busulfan and seizures. Ann Intern Med 1989; 111:543-4.
5. De La Camara R, Tomas JF, Figuera A, Berberana M, Fernandez-Ranada JM. High dose busulfan and seizures. Bone Marrow Transplant 1991; 7:363-4.
6. Grigg AP, Shepherd JD, Phillips GL. Busulphan and phenytoin. Ann Intern Med 1989; 111:1049-50.
7. Vasta S, Scimé R, Indovina A, Majolino I. CNS toxicity and high-dose busulphan in three patients undergoing bone marrow transplantation. (Letter). Haematologica 1992; 77:189.
8. Meloni G, Raucci U, Pinto RM, Spalice A, Vignetti M, Iannetti P. Pretrasplant conditioning with busulfan and cyclophosphamide in acute leukemia patients: neurological and electroencephalographic prospective study. Ann Oncol 1992; 3:145-8.
9. Vassal G, Deroussent A, Hartmann O, et al. Dose-dependent neurotoxicity of high-dose busulfan in children: a clinical and pharmacological study. Cancer Res 1990; 50:6203-7.
10. Browne TR. Clonazepam. A review of a new anticonvulsant drug. Arch Neurol 1976; 33:326-32.

©Ferrata Storti Foundation