Acta Oncologica 27 (1988) Fasc. 5

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VENO-OCCLUSIVE DISEASE IN CHILDREN AFTER INTENSIVE CHEMO- AND RADIOTHERAPY AND REPEATED HALOTHANE ANESTHESIAS

A report of 2 cases

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Abstract

Two cases of veno-occlusive disease (VOD) occurring in metastatic neuroblastoma patients are reported. Treatment included a remission induction by conventional chemotherapy and surgery followed by an early consolidation with massive chemotherapy, total body irradiation and cleared autologous bone marrow transplantation (ABMT). Both patients had multiple halothane anesthesias. Liver complications occurred 10 and 21 days respectively after ABMT. The first patient had a precocious and severe clinical and biological VOD, heparinotherapy and symptomatic treatment were ineffective and he died 12 days after ABMT. The second patient had a moderate and later syndrome which was controlled by heparin therapy (100 U/kg/day) delivered by continuous infusion; he is now alive free of hepatic disturbance 28 months after ABMT. The potential iatrogenic factors are discussed, with special focus on the use of halogenated anesthetic drugs.

Key words: Veno-occlusive disease, neuroblastoma, chemotherapy, total body irradiation, halothane anesthetics.

Veno-occlusive disease (VOD) is a rare clinico-pathological entity, with obscure pathogeny. Classically it is described as a complication of some medical treatments (anticancer, immunosuppressive, oral contraception). Introduction of more and more aggressive therapy in treating some cancers in children, and specially intensive treatment followed by bone marrow transplantation, has been associated with increasing frequency of VOD. Many predisposing factors have been accused during the last few years, such as pre-existing biological liver defects, the use of some anticancer drugs and/or total body irradiation (TBI) (1, 12, 13, 19), and halothane anesthesia (3, 18).

We report two cases of VOD occurring in stage IV neuroblastoma patients who underwent intensive chemotherapy with total body irradiation in our hospital. Both patients were repeatedly subjected to general halothane anesthesia, which can have been an additional risk factor.

The patients were treated according to the French cooperative protocol NB 84 for children more than 1 year old with metastatic neuroblastoma. This treatment involved: 1) induction chemotherapy including sequential cisplatinum-VM 26 (PE) and vincristine-cyclophosphamide-doxorubicin (CAdO) every 3 weeks, with a total of 3 cycles (2), 2) surgical removal of the primary and 3) early systematic consolidation treatment in the first complete or partial remission with intensive therapy, by high-dose vincristine and melphalan, and TBI up to 12 Gy (lung protection after 10 Gy) in 6 fractions and 3 days (14).

The hematological recovery was ensured by transplantation of an immunodepleted autologous bone marrow (ABMT), (5).

Case reports

Case 1. A 13-month-old boy presented in December 1983 with a bulky abdominal neuroblastoma and numerous bone and bone marrow metastases. Liver tests and hepatitis AB serologies were normal at diagnosis. The induction phase was characterized by poor hematological tolerance with several episodes of bacillus septicemia, which lengthened the treatment (7 months) and discrete reversible hepatic cytolysis occurring after every cyclophosphamide course (repeated serological tests remained normal). Nevertheless, bone and bone marrow remission was obtained according to previously described criteria (2, 14), and surgical excision of the primary was performed (stage pT 3 B) (10).

Consolidation treatment was accomplished according to the protocol. Irradiation had to be delivered (twice a day for 3 days) under general anesthesia because of patient's age. At day 10 after

Presented at ECCO-4, Madrid, November 1–4, 1987.

ABMT he got fever, which was not bacteriologically explained and was concomitant with a painful, progressive general hepatomegaly with ascites. Abnormally rapid consumption of transfused platelets and a slight increase of serum transaminase (SGPT: 113 IU/l), total bilirubin (39 mmol/l) and gammaglutamyl-transpeptidase (GT) (65 IU/l) were also noted. Ultrasonography showed homogeneously enlarged liver and reduced diameter of the subhepatic veins. VOD was considered as highly probable and treatment with heparin delivered by continuous infusion at a dose rate of 100 IU/kg/day associated with diuretics and hydric restriction was started. Rapid worsening, marked by increasing ascites and major uncontrolled metabolic disorders led to death at day 12 after ABMT. Autopsy was refused and histological specimen provided by biopsy-needle was unrewarding.

Case 2. A 2-year-old boy, presented in January 1985 with a typical Hutchinson's syndrome, a right-sided supra-renal secreting tumor and bone marrow metastases. The induction phase was marked by good hematological tolerance and discrete hepatic cytolysis with negative serological tests. After surgery (stage pT 3A), the patient achieved complete remission. Consolidation treatment was given according to the protocol during 6 months following diagnosis. General anesthesia with halothane was necessary twice a day for 3 days to deliver TBI. At day 14 after ABMT unexplained fever, weight gain, painful hepatomegaly and progressive ascites appeared. At the same time, the efficiency of platelet transfusions decreased after having previously been satisfactory. Serum transaminase levels raised, but other hepatic tests remained within normal range. Liver ultrasonography was not contributive. Heparin therapy, fluid restriction and diuretic treatment were started without delay. The following course was favorable with decreasing hepatomegaly, ascites and transaminase values within 4 days and a normal temperature after 8 days. The GT level raised temporarily one week later (113 IU/l) but all clinical and biological disorders disappeared 4 weeks after the start of heparin, which was then stopped. This patient is alive 28 months after ABMT with disease, but without evidence of hepatic disorder.

Discussion

In the reported 2 cases, the diagnosis of VOD was based only upon clinical and biological criteria. Liver scintigram and CT (3) could not be performed as patients were isolated under a laminary air flow due to their bone marrow aplasia. Transcutaneous or transvenous liver biopsy (9) was impossible as platelet counts remained too low. Yet, to us the diagnosis seemed to be certain since both patients had painful hepatomegaly with ascites and unexplained fever, and also abnormal platelet consumption combined with biological hepatic abnormalities.

In both cases we find 3 of the factors classically predisposing to an iatrogenic VOD:

– Pre-existence of biological signs of liver disturbance before ABMT (12) which in our patients seemed to be related to drug toxicity; moderate increase of transaminase levels occurred after each cyclophosphamide-vincristine-doxorubicin course, and normalization was observed before every further course. No viral etiology was detected on serological tests. At the time of massive therapy, the preliminary hepatic records were normal.

– Intensive chemotherapy with melphalan. Alkylating agents are supposed to be involved in the occurrence of VOD (1, 8).

– TBI, which can cause liver lesions on its own (11), and certainly increases the risk when combined with cytotoxic drugs in a pre-transplantation conditioning regimen (1, 12, 17).

An additional factor has to be considered, namely the repeated halothane anesthesias. Both our patients underwent 6 short general anesthesias in 3 days, in order to receive TBI. Furthermore, they had been previously anesthetized 14 (patient 1) and 6 (patient 2) times before the consolidation treatment, to perform bone marrow stagings, bone marrow harvesting, to set in central catheters, to remove the primary, and to perform CT scans.

The anesthetics commonly used in children are halogenated compounds, such as halothane. This drug is known for its hepatic toxicity after repeated uses (4) and when associated with anticancer treatments (6, 18) This toxicity is classically an isolated and reversible cytolysis, but very likely it can participate in the induction of VOD.

It seems justified to advocate the limitation of general anesthesias as much as possible, specially with halothane, in children whose treatment program involves intensive therapies, with or wihtout TBI. A very close clinical and biological attention is mandatory in order to detect any sign of VOD at an early stage. The estimation of early parameters, such as factors VII and X, plasminogen and antithrombin III, and N-P3P, have been recently investigated (15, 16) and seems quite interesting for this purpose, especially as other valuable tools for the diagnosis of VOD, such as liver radionuclide scan and liver CT, cannot be performed when patients are in isolation rooms. Experiments conducted in rats have shown that heparin prevents histological lesions associated with liver irradiation (7). Yet, we believe that the systematic institution of heparin therapy at an antiaggregating dose rate, starting with the pre-ABMT conditioning regimen, could be proposed as a way of prevention.

ACKNOWLEDGEMENT

This work was Supported by grant INSERM No. 736400.

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