Defibrotide as a promising treatment for thrombotic thrombocytopenic purpura in patients undergoing bone marrow transplantation

Bone Marrow Transplantation (2002) 29, 542–543. DOI: 10.1038/sj/bmt/1703414

Thrombotic thrombocytopenic purpura (TTP) is a severe microvascular disorder which may occur in 30% to 70% of patients undergoing bone marrow transplantation (BMT) depending on discordant diagnostic criteria. The current retrospective study emphasizes the possible role of defibrotide (DFT), a polydeoxyribonucleotide salt with an antithrombotic and thrombolytic effect, which has been described in the literature. TTP was considered resolved when all clinical and laboratory signs disappeared. Some characteristics of the case series are listed in Table 1. Conditioning regimens included total body irradiation in eight out of 12 patients (TBI 2 Gy twice a day for 3 days) combined with standard cyclophosphamide or with additional drugs, while four out of 12 patients received high-dose cyclophosphamide (CsA) for GVHD prophylaxis at standard doses (in order to maintain the CsA plasma levels around 200–300 ng/ml). Severe TTP was defined according to the above criteria in addition to the central nervous system dysfunction with or without renal impairment and/or the occurrence of gut or bladder bleeding and/or multiorgan failure, with a TTP index (LDH/platelets ratio) >20 (as described in the literature). TTP was considered resolved when all clinical and laboratory signs disappeared. Some characteristics of the case series are listed in Table 1. Conditioning regimens included total body irradiation in eight out of 12 patients (TBI 2 Gy twice a day for 3 days) combined with standard cyclophosphamide or with additional drugs, while four out of 12 patients received high-dose chemotherapy alone. All patients received cyclosporin A (CsA) for GVHD prophylaxis at standard doses (in order to maintain the CsA plasma levels around 200–300 ng/ml), often combined with methotrexate (in 10 out of 12 cases) or other drugs (ATG, steroids, mephitocic microphenolate). Despite this prophylaxis, eight out of 12 cases presented with grade II to IV GVHD. TTP was mild in two patients, and severe in 10; seven out of 10 also developed severe multiorgan hemorrhagic symptoms, especially hemorrhagic cystitis or serious nephropathy which resulted in an increased need for blood products and supportive treatment. TTP was diagnosed at a median of 47 days (range 9–100) after BMT and in six of 12 patients resolved after a median of 23 days (range 14–86). We decided to use DFT for treatment due to the difficulty in performing consecutive plasma exchanges for all 12 patients. DFT therapy started at an average of 2 days (range 1–11) after TTP diagnosis at an average dose of 40 mg/kg p.o. daily (range 30–50) and was discontinued after a median of 41 days (range 17–98). Five out of 12 patients (all died) also received two to three non-consecutive plasmaphereses along with DFT. No patients received plasma. Five out of 12 cases (two mild and three severe) had a complete response in the first 1–3 weeks; one out of 12 cases showed a stabilization of clinical and laboratory signs within 3 months; three out of 12 patients had a partial response; three out of 12 patients did not respond despite prolonged DFT treatment. TTP was not a

References


cause of death in any patient per se: six out of 12 patients died (3/6 non-responders, 3/6 partial responders) because of causes unrelated to TTP (two of interstitial pneumonia, one of interstitial candidiasis, one of pulmonary GVHD, one of gastroenteric GVHD, one of disease progression) at a median of 4 months after BMT (range 2–12). In our experience, DFT was beneficial in about 50% of the patients. It is worth noting that most of our patients suffered from severe TTP and showed a good response to DFT, probably due to the early start of treatment which helped to avoid TTP-related complications. Notwithstanding that the current experience suggests a promising efficacy of DFT in the treatment of post-BMT severe microangiopathy, a multicenter study should be performed in order to draw reliable conclusions.

Acknowledgements

We would like to thank Miss Joanna Upton for her language review, Miss Sara Vaghetti for secretarial services and the Comitato Maria Letizia Verga per lo Studio e la Cura delle Leucemie del Bambino for its continuous support of our research projects.

References

4 Pettitt AR, Clark RE. Thrombotic microangiopathy following bone marrow transplantation. Bone marrow Transplant 1994; 14: 495–504.