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Letter to the Editor

Efficacy of bendamustine as salvage treatment in an heavily pre-treated Hodgkin lymphoma

Bendamustine is a novel-alkylating agent whose mechanisms of action involve induction of apoptosis through activation of DNA-damage stress responses, inhibition of mitotic checkpoints, and induction of mitotic catastrophe. The compound also contains a benzimidazole ring, which may confer purine analogue-like properties in addition to the alkylating capacity. In vitro studies indicate that the DNA repair mechanisms that operate after exposure to the drug are different from those evoked by other agents, potentially explaining observed antitumor effects in cell lines that are resistant to other alkylating agents. It has unique activity against lymphoproliferative disorders, and its favourable side-effect profile makes it amenable for use in combination with other agents [1]. Only few observations are reported on the use of bendamustine in Hodgkin lymphoma (HL) [2–4]. We describe a case of a multi-resistant heavily treated HL patient, which received compassionate use of bendamustine as effective therapeutic regimen.

A 25-year-old man referred to our institution in May 2002 for the sudden onset of cervical adenopathy, fever and nocturnal sweating. A CT scan revealed bilateral supraclavear and cervical adenopathy, involvement of mediastinal adenopathy and para-aortic lymph nodes. After biopsy, a diagnosis of nodular sclerosis classical Hodgkin disease stage IIIB was made. He received 8 cycles of combination chemotherapy consisting of adriamycin, bleomycin, vinblastine and dacarbazine (ABVD) from May to December 2002, but the final re-evaluation showed a progression of disease. He received salvage therapy with iphosphamide, etoposide, epirubicin (IEV schedule) and two subsequent cycles containing bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP schedule) obtaining a partial response. He received peripheral autologous stem cell transplantation, but after 4 months a PET-CT scan revealed a persistent para-aortic localization and increased metabolic activity in left kidney. He received then six cycles of chemotherapy according to BEACOPP schedule. A PET-CT scan after the sixth cycle showed mediastinal and abdominal localizations. Salvage therapy with dexamethasone, cisplatinum, cytarabine (DHAP schedule) and mediastinal radiotherapy was performed from July to October 2004. In April 2005 a PET-CT scan revealed a new progression of disease with increased activity in the liver and the bone. In May 2005 he was started on gemcitabine and vinblastine schedule treatment, which was performed from May to September 2005, when a CT scan re-evaluation showed a progression of disease with bilateral lung infiltration. He was rescued with sixth line chemotherapy according to PROVECIP schedule (vinblastine, procarbazine, cyclophosphamide, prednisone) until June 2006, when a PET-CT scan revealed a persistence of metabolic activity in the left lung and in the right humerus. For the persistence of disease the patient was maintained, from March 2007 to December 2007, with VBM schedule (vinblastine, bleomicine, methotrexate) and then, from February 2008 to March 2009 with chlorambucil associated to cyclophosphamide. In April 2009, in the presence of fever and fatigue, a CT scan revealed a further mediastinal and lung progression. Bendamustine, as a compassionate program, was used as single agent at the dose of 90 mg/m^2 for two consecutive days. An informed consent was obtained by the patient for this treatment program, which was formally approved by the hospital Ethical Committee. After the fourth cycle, a PET-CT scan revealed, for the first time, a complete regression of the previously described lesions. In Fig. 1, PET-FDG pre- (a) and post-bendamustine treatment (b) is shown. This result was consolidated with two other courses of the same treatment. Unfortunately, after 6 months of unmaintained response, the patient experienced a new relapse of the disease with supra- and sub-diaphragmatic localizations.

The clinical activity of bendamustine has been reported in various malignant lymphomas including low, intermediate, and high-grade non-Hodgkin lymphomas (NHL), chronic lymphocytic leukemia and multiple myeloma. Nevertheless, in the specific setting of Hodgkin lymphoma only few, and very old contributions are available: in 1975 a German study on untreated patients reported a response in 7/10 of them. In a study published in 1984 Hoche et al. incorporated bendamustine in a complex polychemotherapy regimen, which did not show significant advantages as compared to COPP [3]. In 1987, Harold et al. published in Germany an experience in which bendamustine was introduced into the second-line therapy of HL in patients who were refractory to primary COPP schedule (cyclophosphamide, vincristine, procarbazine, prednisone). Bendamustine was combined with daunorubicin, bleomycin and vincristine (DBVCRB schedule), and compared to a modified ABVD schedule in 73 patients: no differences in the remission rate (RR: 68% vs. 83%), in the duration of remission or median survival time were reported [2]. In recent times only one experience is available as meeting report: bendamustine was employed as single agent (120 mg/mq in two consecutive days every 28 days) in relapsed/refractory HL patients. Eighteen patients were enrolled: of these 2 died rapidly before the re-evaluation, whereas 12 out of 14 evaluable patients responded. Six patients (38%) obtained a complete response and 6 patients (38%) a partial response after the first re-staging [5].

In our experience bendamustine documented a complete response with no evidence of disease at CT scan and FDG-PET in a patient in which no one of the 7 previous lines of treatment, including an autologous stem cell transplantation, could obtain such as a result.

Bendamustine activity strongly needs to be further investigated in HL patients.

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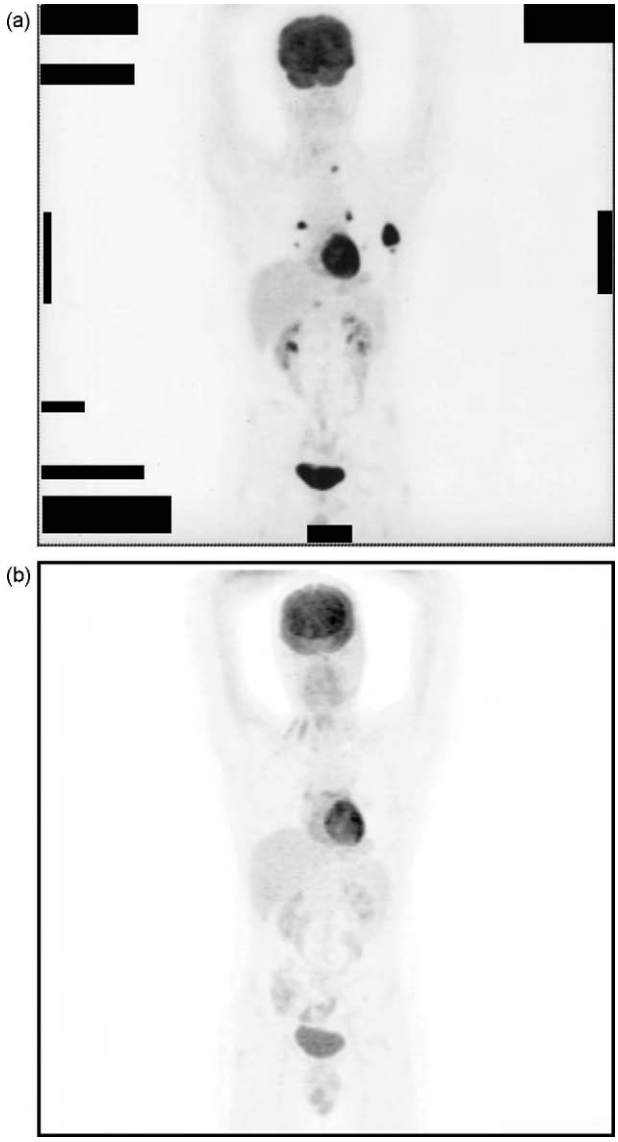

Fig. 1. (a) FDG-PET scan, performed before bendamustine treatment, shows multiple pathological captation areas in neck and thoracic region. (b) Absence of pathological activity after 4 cycles of bendamustine at FDG-PET scan.

Conflict of interest

All authors have no conflict of interest to report.

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