



ESHAP chemotherapy regimen associated to lenalidomide induces complete isotopic remission in Hodgkin's lymphoma relapsing after autologous stem cell transplantation

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Abstract: Hodgkin's lymphoma is a highly curable disease with a majority of patients presenting in early stages of disease. For those patients relapsing after the first line of chemotherapy, several regimens have been proposed, all of which were followed by ABSCT (autologous blood stem cell transpaltation). Those late-stage patients who relapse after ABSCT have a very poor prognosis. In our heavily pre-treated patients, ESHAP chemotherapy, in conjunction with Lenalidomide treatment, resulted in complete isotopic remission.

Response to Reviewers: Dear Editor, Dear Reviewer,

You can find here the suggested list of changes:

1. The time to relapse after BEAM was added as a new column at table one
2. Evaluation of responses was made by combined CT and 18F-FDG PET scan, using the International Harmonisation Project Criteria

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Running Title: Hodgkin lymphoma, relapse, lenalidomide

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1. The time to relapse after BEAM was added as a new column at table one

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Dear Editor,

Hodgkin's lymphoma is a rare human cancer characterised by a high rate of curability during the early stages of the disease. Despite the good results obtained with chemotherapy and radiotherapy, patients with advanced disease have a poor prognosis, especially those who relapse after autologous stem cell transplantation. These patients are rarely cured by a classical regimen of chemo- or radiotherapy. Several new strategies and drugs are under investigation based on the newest discoveries in disease biology. We treated three Hodgkin patients who had relapsed after high-dose chemotherapy and autologous stem cell transplantation with ESHAP (Etoposide, Cytarabin, Cisplatin and Methylpredisolone) chemotherapy and Lenalidomide, and their response was evaluated by 18F-FDG PET scan after three cycles. Because three complete isotopic responses were obtained, these patients could continue their therapeutic program via allogenic stem cell transplantation.

During a period of one year, we identified three Hodgkin's lymphoma patients who relapsed after autologous stem cell transplantation. The median age of the patients was 36 years. The characteristics of these three patients are presented in table 1.

Patient	Age	Time to relapse after BEAM (months)	Initial stage	Initial treatment	Nr of cycles ESHAP Rev	Stage at relapse	line of TT	Anemia	Neutropenia	Thrombocytopenia
1	37	42	4	2ABVD, 2 MOPP BEAM	2	2	4	grade 2	grade 3	grade 3
2	40	3	4	2ABVD+ 3VABEM+ BEAM+ RxT	3	4	5	grade 3	grade 4	grade 4
3	31	30	2	6ABVD+ 2VABEM+ 1MINE+ BEAM+ RxT+ 4MINE+ 8MOPP	3	4	7	grade 3	grade 4	grade 4

ABVD – Adriamycin, Bleomycin, Vincristin, Dacarbazine
MOPP – Mechlorethamin, Procarbazine, Vincristin, Prednisone
VABEM – Vincristin, Adriamycin, BCNU, Etoposide, Methylprednisolone
BEAM – BCNU, Etoposide, ARA-C, Melphalan
MINE – Navelbine, Ifosfamide, Mitoguanine, Etoposide
RxT – Radiotherapy

Table 1 – Characteristics of patients with Hodgkin's lymphoma relapsing after ABSCT and treated with ESHAP – Revlimid and the toxic effects of the regimen

Each patient was heavily pre-treated before and after relapse with at least four lines of chemo- and radiotherapy. The patients were treated with an ESHAP chemotherapy regimen once every three weeks and with Lenalidomide 15 mg daily. Lenalidomide was selected because of its anti-angiogenic effects as well as its abilities to induce apoptosis via p21 and cell cycle arrest and recruit effector T and NK cells. The patients gave their informed consent to be treated with Lenalidomide. On day 8 of each course of chemotherapy, all patients received primary G-CSF prophylaxis in a treatment regimen of 5 µg/kg/day for five days to prevent neutropenia. The adverse effects of this regimen were grade 4 neutropenia despite the presence of G-CSF and thrombocytopenia that required platelet transfusion. Eighteen days

after the end of the third (second in one patient) cycle of chemotherapy, the patient response was evaluated by combined CT and 18F-FDG PET scan, using the International Harmonisation Project Criteria, and three complete isotopic responses were observed. Because the good responses obtained, the patients could continue the therapeutic program and became candidates for allogenic stem cell transplantation in good conditions.

Hodgkin's lymphoma is a highly curable disease with a majority of patients presenting in early stages of disease and responding to the gold standard, anthracyclin-based ABVD chemotherapy (1, 2). Patients with an advanced stage of the disease have an high failure rate using standard therapy (3); these patients require more intensive strategies, most of which are based on high-dose chemotherapy, with or without autologous stem cell support (4,5,6,7). For those patients relapsing after the first line of chemotherapy, several regimens have been proposed, all of which were followed by ABSCT (autologous blood stem cell transpaltation). Those late-stage patients who relapse after ABSCT have a very poor prognosis. The majority of these patients underwent allogenic stem cell transplantation because of their young age (8, 9). Unfortunately, there is no standard therapy for patients who relapse after ABSCT and will subsequently undergo AlloSCT. New discoveries leading to a better understanding of Hodgkin's disease has allowed new treatment strategies to be developed (10). One compound that is being tested is Lenalidomide, a powerful Thalidomide analogue. Previously, Reed-Sternberg cells were shown to be dependent on their microenvironment such that their culture is very difficult once removed from their "home" (11). Lenalidomide has several effects on the tumour microenvironment and its growth: antiangiogenic effects, immunomodulation via alterations in cytokine production, activation of T-cells, augmentation of NK cell activity and direct anti-tumour activity by cell cycle arrest and the induction of apoptosis (12). Recently, two trials used Lenalidomide as a single agent to treat patients with refractory or relapsed Hodgkin disease, with interesting results. Some patients responded to the treatment, and others experienced a stabilisation of their disease (13, 14). In our heavily pre-treated patients, ESHAP chemotherapy, in conjunction with Lenalidomide treatment, resulted in complete isotopic remission. In addition, the side effects were acceptable, which allowed the patients to remain in good condition while they continued their therapeutic program along with the allogenic stem cell transplantation.

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