American Journal of Therapeutics 13, 556–557 (2006)

Relapse of High-Grade Non-Hodgkin's Lymphoma After Autologous Stem Cell Transplantation: A Case Successfully Treated With Cyclophosphamide Plus Somatostatin, Bromocriptine, Melatonin, Retinoids, and ACTH

Mauro Todisco, MD*

Patients with relapse of high-grade non-Hodgkin lymphoma (NHL) after autologous stem cell transplantation (auto-SCT) generally have a poor prognosis. Only a minority of these patients can be cured by a second myeloablative chemotherapy, and conventional salvage treatments are often associated with severe toxicities. With a combination of cyclophosphamide, somatostatin, bromocriptine, retinoids, melatonin, and ACTH, we already reported 100% global response in 8 patients with relapse of low-grade NHL after single or combined chemotherapy and a therapy-free period of ≥6 months. This provided the rationale to evaluate the same pharmacological association in a patient with relapse of high-grade NHL after auto-SCT performed 2 years before. The patient was treated for at least 2 months. At the end of this period, if he had stable or responding disease, he received additional 3 months of treatment, and if he was stable or responding after 5 month, he was treated for 3 months and more. After 2 months, patient had a partial response, and after 5 months, he achieved a complete response. Today, 14 months after beginning treatment, patient is in complete remission. Treatment had very good tolerance, and patient carried on at home doing his normal activities. Our result and severe toxicities associated with conventional salvage treatments suggest in a relapse of high-grade NHL after auto-SCT, further clinical trials using the pharmacological association we employed in this case.

Keywords: High-grade non Hodgkins, lymphoma, melatonin, fomatostatin, cyclophosphamide, retinoids

INTRODUCTION

In 1979, Di Bella et al[1] reported to have favorably administered cyclophosphamide together with somatostatin, bromocriptine, retinoids, melatonin, and ACTH in several cancers including non-Hodgkin lymphoma (NHL).

With the same pharmacological association that we already described, there was 100% of global response (50% complete response and 50% partial response) in 8 patients with relapse of low-grade NHL after single or combined chemotherapy and a therapy-free period of ≥6 months.[2] This provided the rationale to treat with cyclophosphamide plus somatostatin, bromocriptine, retinoids, melatonin, and ACTH a patient with relapse of high-grade NHL after cytoreductive regimen and autologous stem cell transplantation (auto-SCT) performed 2 years before.

METHODS

Treatment

The patient received a combination of cyclophosphamide, somatostatin, bromocriptine, retinoids, melatonin, and ACTH. Cyclophosphamide was given orally

ASL 11, Local Health Department of National Health Service, Fermo, Italy.
**Address for correspondence: via Crivelli 40, 63013 Grottammare (AP), Italy. E-mail: todmau@tin.it*

at a total daily dose of 100 mg/d (50 mg at 2 PM and 50 mg at 9 PM). Somatostatin was administered subcutaneously at a dose of 3 mg/d within 8 hours using a syringe pump. The administration started at least 3 hours after dinner. Bromocriptine was given orally at a dose of 2.5 mg/d (1.25 mg at 2 PM and 1.25 mg at 9 PM). For retinoids, all-*trans* retinoic acid, vitamin A palmitate, and beta-carotene were administered orally, at 8 AM, in 5 mL of vitamin E, respectively, at doses of 5 mg, 5000 UI, and 20 mg/d. Melatonin was given orally at a dose of 20 mg/d (10 mg at 2 PM and at 9 PM). ACTH was administered intermuscularly at a dose of 0.5 mg twice weekly. Patient was treated for at least 2 months. At the end of this period, if his disease was stable or responding, he received an additional 3 months of treatment, and if he was stable or responding after 5 months, he was treated for 3 months and more.

Criteria for response

Complete response or remission was defined as the complete disappearance of all the measurable or detectable lymphomatous lesions as demonstrated by physical examination, chest radiograph, ecotomography, computed tomography or magnetic resonance imaging, and positron emission tomography (PET). Partial response was defined as a $\geq$50% reduction in the sum of the products of the 2 diameters (the longest diameter and the one perpendicular to it) of $\geq$1 lesions lasting at least 4 weeks with a concurrent significant reduction in fluorodeoxyglucose (FDG) uptake on serial whole-body PET scans. Progression was defined by the increase in size of the preexisting lesions of at least 25% and/or by a significant increase in their FDG uptake on serial whole-body PET scans, the onset of new measurable or detectable lesions, or an increase in spleen or liver size of at least 2 cm due to lymphoma.

Situations that could not be clearly placed in any of the described categories were defined as a stable condition. The assessment of response was made after 2 months from the beginning of the treatment and, later, every 3 months.

CASE REPORT

A 39-year-old man was diagnosed with a large-cell B NHL stage IVA in November 2000. From November 2000 to March 2001, patient obtained a complete response with multiple phases of a cytoreductive regimen including CHOP, rituximab, and DHAP; then he received sequential high-dose chemotherapy with auto-SCT. Afterward, the patient was included in a program of longitudinal controls from which a complete response resulted until January 2004, when a PET showed a pathologic uptake in the spleen, retroperitoneal lymph nodes, and L4. Computed tomographic and magnetic resonance imaging scans confirmed the relapse of disease. The patient began a treatment with cyclophosphamide plus somatostatin, bromocriptine, retinoids, melatonin, and ACTH in March 2004. After 2 months, a PET revealed a significant reduction in FDG uptake.

A complete response was documented after a further 3 months through computed tomographic and magnetic resonance imaging scans and a new PET.

Today, 14 months after the beginning of treatment, patient is in complete remission.

The administered pharmacological association had very good tolerance, and the patient carried on at home doing his normal activities.

DISCUSSION

Patients with a relapse of high-grade NHL after auto-SCT generally have a poor prognosis.[3] A minority can be cured by a second course of myeloablative chemotherapy at the cost, however, of high-risk toxicity.[4]

With an association of cyclophosphamide, somatostatin, bromocriptine, retinoids, melatonin, and ACTH, we have documented a complete response in a patient who had a relapse of high-grade NHL 2 years after an auto-SCT.

Our result and the severe toxicity associated with conventional salvage treatments suggest that in a relapse of high-grade NHL after auto-SCT there should be further clinical trials using the pharmacological association that we employed in this case.

REFERENCES

1. Di Bella L, Rossi MT, Scalera G. Perspectives in pineal functions. In: Ariens Kapperrs J, Pévet P, eds. The Pineal Gland in Vertebrates Including Man. Amsterdam: Elsevier North-Holland Biomedical Press; 1979:475–478.
2. Todisco M, Casaccia P, Rossi N. Cyclophosphamide plus somatostatin, bromocriptine, retinoids, melatonin and ACTH in the treatment of low-grade non Hodgkin's lymphomas at advanced stage: result of a phase II trial. *Cancer Biother Radiopharm*. 2001;16:171–177.
3. Buchler T, Hermosilla M, Ferra C, et al. Outcome and toxicity of salvage treatment on patients relapsing after autologous hematopoietic stem cell transplantation—experience from a single center. *Hematology.* 2003;8: 145–150.
4. Lenain C, Dumontet C, Gargi T, et al. Second autologous transplantation after failure of a first autologous transplant in 18 patients with non Hodgkin's lymphoma. *Hematol J*. 2004;5:403–409.