

Low-grade Non-Hodgkin Lymphoma at Advanced Stage: A Case Successfully Treated With Cyclophosphamide Plus Somatostatin, Bromocriptine, Retinoids, and Melatonin

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Low-grade non-Hodgkin lymphomas (NHLs) at advanced stage are still incurable, and treatment may include chemotherapy with a single drug or a combination of different drugs. With a combination of cyclophosphamide, somatostatin, bromocriptin, retinoids, melatonin, and adrenocorticotropic hormone, we already reported 100% of global response (50% complete response and 50% partial response) in 12 patients with low-grade NHL at advanced stage: 4 previously untreated patients and 8 with relapse of disease after single or combined chemotherapy and therapy free time ≥ 6 months. This provided the rationale to treat a patient affected by low-grade NHL stage 4, with cyclophosphamide, somatostatin, bromocriptin, retinoids, and melatonin (adrenocorticotropic hormone was not administered for high blood pressure). The patient was treated for at least 2 months. After this period, if he had stable or responding disease, 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. After 2 months the patient had a partial response, and after 5 months he achieved a complete response. Today, 18 months after the beginning of treatment, the patient is in complete remission. Treatment had very good tolerance, and the patient carried on at home doing his normal activities.

Keywords: non-Hodgkin lymphoma, cyclophosphamide, somatostatin, retinoids, melatonin

INTRODUCTION

In 1979 Di Bella et al¹ reported to have favorably administered a combination of somatostatin, bromocriptine, retinoids, melatonin, adrenocorticotropic hormone (ACTH), and cyclophosphamide in several cancers including non-Hodgkin lymphoma (NHL). In 1984 Payan et al² demonstrated that somatostatin inhibits the growth of cultured primary human lymphocytes and Molt-4 cells, in 1987 Nakamura et al³ identified somatostatin receptors on the membrane of several lymphoid cell lines, and in 1990 Hiruma et al⁴ found somatostatin receptors on primary leukaemia human cells. In 1995 Witzig et al⁵ reported that

octreotide, a somatostatin analog, shows activity in patients with low-grade NHL. The influence on lymphatic growth has also been demonstrated for prolactin, retinoids, melatonin, and ACTH. Prolactin stimulates the growth of experimental lymphomas both in vivo and in vitro⁶; furthermore, in 1997 Matera et al⁷ demonstrated that prolactin is an autocrine growth factor for a human leukemic cell line. Retinoids have a therapeutic effect not only in promyelocytic leukaemia, but also in T and B cell lymphomas.^{8–11} Melatonin inhibits thymidine incorporation as in normal lymphocytes as in lymphoblastoid cell lines,¹² and inhibits the proliferative response to mitogens.¹³ In addition, melatonin carries on an antimyelodysplastic action and decreases the bone marrow toxicity of chemotherapeutic agents.¹⁴

ACTH receptors are expressed on the cell surface of T and B lymphocytes,¹⁵ and ACTH depresses the lymphocyte blastogenesis in response to phytoemagglutinin and concanavallin A.¹⁶ All these studies,

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together with the well-known action of cyclophosphamide, provided us the rationale to design a phase 2 study to determine if a combined therapy on the basis of cyclophosphamide, somatostatin, bromocriptin, retinoids, melatonin, and ACTH had activity in patients with low-grade NHL at advanced stage.

In 2001, we reported that such a regimen may be safe and effective in low-grade NHLs at advanced stage, obtaining 100% of global response (50% complete response and 50% partial response) in 12 patients with low-grade NHL at advanced stage: 4 previously untreated patients and 8 with relapse of disease after single or combined chemotherapy and therapy free time ≥ 6 months.¹⁷ On the basis of these results we treated with the same regimen a patient affected by low-grade NHL stage 4 (ACTH was not administered for high blood pressure).

METHODS

Treatment

The patient, a 58-year-old woman, received a combination of cyclophosphamide, somatostatin, bromocriptine, retinoids, and melatonin. Cyclophosphamide was given orally at a total daily dose of 75 mg/d (50 mg at 2 PM and 25 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). The patient was treated for at least 2 months. At the end of this period, if her disease was stable or responding, she received an additional 3 months of treatment, and if disease was stable or responding after 5 months, she 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, echotomography, computed tomographic or magnetic resonance scans, positron emission tomography (PET), and bone marrow biopsy. 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 ≥ 1 lesions lasting at least 4 weeks and/or a reduction

in fluorodeoxyglucose 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 fluorodeoxyglucose 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 owing to lymphoma. Situations that could not be clearly placed in any of the described categories was 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 58-year-old woman was diagnosed with a low-grade NHL stage 4 in May 2004, the lymphomatous lesions being localized in spleen, bone marrow, and subdiaphragmatic, axillar, laterocervical lymph nodes. In July 2004, the need to start a treatment was expressed by doctors of the Department of Hematology that followed the patient, the disease being in progression for the appearance of a new submandibular adenopathy of about 5 cm with contextual flogistic edema of the cheek. The patient chose to follow our treatment with cyclophosphamide, somatostatin, bromocriptine, retinoids, and melatonin.

After 2 months the patient had a partial response. A complete response was documented after a further 3 months through bone marrow biopsy and echotomography.

Today, 18 months after the beginning of treatment, the 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

The low-grade NHL at advanced stage are still incurable, and treatment may include chemotherapy with a single drug or a combination of several different drugs. Single-agent chemotherapy with alkylants has been described to realize 36% of global response, with 5% of complete response, in 132 previously untreated patients, although 60% of global response in 127 previously untreated patients has been described with widely used chemotherapy as Cyclophosphamide Adriamycin Vincristine Prednisone (CHOP).¹⁸ Octreotide, a somatostatin analogue, has been described to realize 36% of partial response in 28 previously treated and untreated patients.⁵

With a combination of cyclophosphamide, somatostatin, bromocriptin, retinoids, melatonin, and ACTH, we already described 100% of global response (50% complete response and 50% partial response) in 12 patients with low-grade NHL at advanced stage: 4 previously untreated patients and 8 with relapse of disease after single or combined chemotherapy and therapy free time ≥ 6 months⁶; this was a better result of that obtained with single constituents of this pharmacological association.

This provided the rationale to treat with the same association a patient affected by low-grade NHL stage 4 (ACTH was not administered for high blood pressure). After 5 months, this patient also achieved a complete response, and today, 18 months after the beginning of treatment, the patient is in complete remission. The administered pharmacological association had very good tolerance, and the patient carried on at home doing his normal activities.

This result confirms our previous observations, and suggests, in low-grade NHL at advanced stage, further clinical trials using the pharmacological association that we already described.

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