



Clinical Investigation

PLACE OF LOW-DOSE TOTAL BODY IRRADIATION IN THE TREATMENT OF LOCALIZED FOLLICULAR NON-HODGKIN'S LYMPHOMA: RESULTS OF A PILOT STUDY

PIERRE M. RICHAUD, M.D.,* PIERRE SOUBEYRAN, M.D.,† HOUCHINGUE EGHBALL, M.D.,† BOSCO CHACON, M.D.,* GÉRALD MARIT, M.D.,† ANTOINE BROUSTET, M.D.‡ AND BERNARD HOERNI, M.D.†

Departments of *Radiation Oncology and †Medicine, Institut Bergonié, Regional Cancer Center, 33076 Bordeaux Cedex, France; and ‡Department of Haematology, Hôpital du Haut-Lévêque, 33604 Pessac, France

Purpose: In a first prospective nonrandomized trial, 107 patients with Stage III and IV "low-grade" lymphomas have been treated with a combination of chemotherapy and low-dose total body irradiation (LD-TBI). This study shows that this scheme of LD-TBI was very well tolerated, gave a high response rate (83%), and extended RFS. It incited us to start a pilot study on localized follicular lymphomas.

Methods and Materials: From January 1986 through October 1994, 34 patients with previously untreated localized low-grade nonHodgkin's lymphomas have been included in a prospective trial with LD-TBI followed by radical involved field radiotherapy (IF-RT). Patients received two courses of whole body irradiation of 0.75 Gy in 5 fractions and 1 week separated by a rest period of 2 weeks. After 1 month, patients were reevaluated, and received 40 Gy in 20 fractions, and 4 weeks on initially pathological lymph node areas. Eight patients have been excluded from the study: 4 after histologic review (2 centrocytic, 1 lymphocytic, 1 centroblastic) and 4 patients with Stage IV because of bone-marrow involvement. The remaining 26 patients were 11 men and 15 women, 50 years old median age (mean: 50.2; range: 35-73.5) with clinical Stage I (10 pts), III (8 pts), and II2 (8 pts). All patients received the planned treatment.

Results: Clinical tolerance was excellent, and the hematological follow-up shows a mean nadir value of 3.9.10⁹/l (2.1-8.1) for leucocytes, 13.4 g/l (10.8-15.4) for hemoglobin, and 124.10⁹/l (46-216) for platelets, with a median delay of 3.2 months. Of 26 patients, 24 achieved complete remission (CR) after the LD-TBI that was before the IF-RT. All patients, except one, were in complete remission after IF-RT. Nineteen patients remain alive without any evidence of disease, with a median follow-up of 56.2 months. Five patients relapsed; 3 of them died.

Conclusion: As delivered, this schedule of LD-TBI give a very high rate of CR in localized follicular non-Hodgkin's lymphoma, with a very good tolerance. It remains to prove that this immediate efficacy has an impact on long-term disease-free survival in such patients, and to understand how the LD-TBI works (direct and/or indirect induction of apoptosis; relationship with t(14;18) translocation and overexpression of bcl-2). These will be the two aims of a new EORTC prospective randomized trial comparing LD-TBI followed by IF-RT vs. IF-RT alone. © 1998 Elsevier Science Inc.

Follicular lymphoma, Low-dose total body irradiation, Apoptosis.

INTRODUCTION

Low-dose fractionated total body irradiation has been used since the beginning of this century (7). During the 1970s, Johnson (13) and Del Regato (6) published the first encouraging results in the treatment of chronic lymphocytic leukemia and other hematological malignancies. More recently, several studies showed that LD-TBI is one of the first-line treatments in advanced stage low-grade non-Hodgkin's lymphoma (1, 5, 20, 22, 24).

In a first prospective trial, we treated 107 patients with Stage III and IV "low-grade" lymphoma with a combination of chemotherapy (CVP or CHOP) and LD-TBI (33). This study showed that this LD-TBI scheme was very well

tolerated, gave a high response rate (83%), and extended RFS. Up to now, no adjuvant therapy (neither neoadjuvant chemotherapy nor other maintenance therapy) has produced any improvement in survival of such patients. It incited us to initiate a pilot study on localized follicular lymphoma.

METHODS AND MATERIALS

From January 1986 through October 1994, 34 previously untreated patients with localized low-grade follicular lymphomas were treated by low-dose total body irradiation (LD-TBI) followed by radical involved-field radiotherapy (IF-RT).

Reprint requests to: Pierre M. Richaud, M.D., Department of Radiation Oncology, Institut Bergonié, Regional Cancer Center,

180, rue de Saint-Genès, 33076 Bordeaux Cedex, France. Accepted for publication 31 July 1997.

Pathological diagnoses were reviewed, leading to withdrawal of 4 patients (2 centrocytic, 1 lymphocytic, 1 centroblastic). Four other patients were Stage IV with obvious bone-marrow involvement. The remaining 26 patients were 11 men and 15 women; their median age was 50 years (mean: 50 years), ranging from 35 to 73.5 years, with a performance status ≤ 1 . In all cases, the diagnosis was confirmed either as centroblastic-centrocytic lymphoma as defined in the Kiel classification (19), or as predominantly small cleaved cell or mixed small cleaved and large cell in the Working Formulation (39).

Clinical staging was performed according to the criteria of Ann Arbor Conference (3): 10 patients presented with clinical Stage I, 8 patients with Stage III, and 8 patients with Stage II.

Total body irradiation was the first treatment for all patients. The technique has already been described (32). The treatment schedule included 2 courses of LD-TBI of .75 Gy given in 5 fractions/1 week separated by a rest period of 2 weeks. Four weeks later, initially involved areas were irradiated to a total dose of 40 Gy in 20 fractions and, 4 weeks later, either by 25 MV photons or by γ -rays according to the lymph node locations.

All patients received the planned treatment without any delay.

Evaluation was performed 4 weeks after completion of LD-TBI, at the end of IF-RT, and 6 weeks after the completion of treatment. Afterwards, all patients were regularly seen every 3 months for the first 3 years, and every 6 months the next 2 years, and then yearly.

No patients were lost to follow-up. Overall survival (OS) was calculated from the date of pathological diagnosis. Time to relapse (TTR) was calculated from the date of the end of treatment; the date of relapse is defined as the date of its first manifestation. Survival and TTR curves were computed using the Kaplan-Meier actuarial method. Median follow-up was 52.6 months (range: 22 to 126 months).

RESULTS

The tolerance of LD-TBI was excellent: 9 patients complained of mild asthenia and/or anorexia. From a hematologic point of view, the mean observed nadir value after completion of treatment has been $3.9 \cdot 10^9/l$ (range: 2.1 to $8.1 \cdot 10^9/l$) for granulocyte count, 13.4 g/l (10.8 to $15.4 \cdot 10^9/l$) for hemoglobin level, and $124 \cdot 10^9/l$ (46 to $216 \cdot 10^9/l$) for platelet count with a mean duration of 3.2 months. No delay in the planned treatment was observed for the LD-TBI nor for the IF-RT. No acute nonlymphoblastic leukemia or myelodysplastic syndrome occurred in our series.

Of 26 patients, 24 were in complete clinical remission after the LD-TBI, and before the IF-RT: 1 patient experienced a tumor regression more than 75% on lymphangiogram and CT scan, and was considered in complete remission only after the subdiaphragmatic irradiation. The other presented a diffuse progressive disease during the 2-week rest period between the 2 courses of TBI. He had initially a

Stage I cervical node but, unfortunately, a new biopsy was not performed at the time of relapse. Nineteen patients remain alive without any evidence of disease, with a median follow-up of 52.6 months. Five patients relapsed; 3 of them died. Four patients relapsed in nodes areas outside the fields of radical radiation therapy and 1 patient presented with bone-marrow involvement, then leukemic failure. Two other patients died from intercurrent disease, 12 and 13 months after the completion of treatment while in complete remission (1 from diabetic encephalitis, the other from epidermoid carcinoma of oral cavity). The 5-year time to relapse and overall survival are, respectively, 66% and 60%.

DISCUSSION

This is the first prospective study evaluating LD-TBI efficacy in limited-stage follicular lymphoma.

The follicular lymphomas are the most common of all nonHodgkin's lymphomas. They represent a well-defined entity from a biological and clinical point of view. Arising from follicular B cells, their involvement is typically confined to abnormal follicles that totally destroy the normal lymph-node architecture. Most of them (85%) present with a t(14;18) translocation (16).

Clinically, regional disease presentations of follicular lymphoma (clinical Stages I and II) are important to recognize because radiation therapy of all involved lymph-node areas may be highly effective in achieving long-term disease control, as well as prolonged disease-free survival (36).

Approximately 50% of patients with localized Stage II disease and 65% of patients with Stage I disease remain free of disease 10 years after treatment (29). The overall survival rate for Stage I and II disease varies from 60 to 80% at 10 years. However, their evolution is studded with relapses, most of them within the first 5 to 6 years after treatment, usually in unirradiated areas (18, 21, 35, 38, 41). All attempts to reinforce treatment have shown no survival improvement until now.

Total nodal irradiation (TNI) does not seem to improve survival with regard to involved field radiation therapy (IFRT): the 1975-1980 EORTC controlled lymphoma trial did not show any difference between regional RT (10 patients), and extended RT (10 patients) for patients with Stage II follicular cell-pattern lymphoma (4). However, in a prospective study from Stanford, Paryani *et al.* (28) noted that TNI produced a significantly better rate of freedom from relapse (FFR) than IFRT (85% vs. 45% at 10 years, $p = 0.002$) for laparotomy Stages I and II patients. A recent update of the Stanford trial suggests a better outcome with TNI or better outcomes in patients who have laparotomy staging, suggesting that the degree of treatment in these patients is related to the degree of staging.

The addition of chemotherapy in early stage disease, although improving progression-free survival, has not been shown to improve overall survival (17, 20, 25, 27). A prospective randomized trial reported by Monfardini *et al.* in pathologically Staged I and II LGNHL comparing no

further treatment to 6 cycles of COP after radiotherapy demonstrated no difference in progression-free survival (PFS) or overall survival (OS) at 5 years (25). Yahalom *et al.* (42) confirmed no improvement in PFS or OS by the addition of CHOP chemotherapy for Stage I disease patients achieving a complete remission to local radiotherapy.

The British National Lymphoma Investigation group randomized 148 patients after radiotherapy between no further treatment and chlorambucil: no difference in PFS and OS was found. The EORTC study showed, with a limited number of patients (28), a higher 5-year PFS for patients with CVP adjuvant chemotherapy ($p = 0.06$), but no difference in OS.

In the absence of an overall survival benefit, there is no clear role for adjuvant chemotherapy in follicular lymphomas, whatever the number of drugs or the length of time for which they are given.

Therefore, at the present time, the situation is:

- Involved field radiation therapy is highly effective in achieving local control;
- in almost 50% of patients with favorable disease presentations, such irradiation appears to be potentially curative;
- surgical staging by exploratory laparotomy appears unnecessary;
- more extensive irradiation does not appear to improve results in favorable patients.

Low-dose TBI has been used a long time (12) in the treatment of hematologic malignancies, and especially in low-grade malignant lymphomas (5, 13, 31, 32). Previous experiences have shown interest in the management of low-grade disseminated (Stages III and IV) follicular lymphomas, alone or in combination with chemotherapy (11, 20, 22, 24, 33).

In a first prospective nonrandomized trial, we showed the feasibility and good tolerance of this simple schedule of LD-TBI delivering 2 courses of .75 Gy in 5 fractions and 1 week, separated by a rest period of 2 weeks (33). It appeared, also, that the best response following LD-TBI was obtained in follicular lymphoma. In this series, in 70 patients with a survival more than 2 years and treated since 1977 by LD-TBI + chemotherapy (CVP or CHOP) ± localized RT, we did not observe any acute

nonlymphoblastic leukemia or myelodysplastic syndrome with a median follow-up of 88 months (40).

This pilot study of LD-TBI in localized follicular lymphoma strengthens the results, with a high rate of complete clinical remission and an excellent tolerance. However, it remains to prove that this immediate efficacy has an impact on long-term disease-free survival in such patients.

Another question mooted by this study is to understand how LD-TBI works: it is unlikely that such low-dose radiation works as usual doses of radiation by the way of double-strand breaks in DNA and cellular necrosis. We know that most follicular lymphomas present with a t(14;18) translocation. The bcl-2 gene from chromosome 18 is translocated to joined region of the immunoglobulin heavy chain gene on chromosome 14. The immunoglobulin heavy chain gene enhancer, which normally allows for amplified transcription of the immunoglobulin on antigenic stimulus, appears to also allow transcription of bcl-2, resulting in constitutive production of bcl-2 protein along with the heavy chain immunoglobulin (34). Methods of detection, including surface marker analysis, immunoglobulin gene rearrangement, molecular probes for t(14;18) and bcl-2 oncogene, using polymerase chain reaction (PCR) methods in peripheral blood, lymph node, and/or bone marrow may detect as few as one abnormal cell in 100,000 cells (2, 8, 9, 14, 15, 23, 26, 30, 37). The bcl-2 protein is a mitochondrial protein that inhibits apoptosis (10). The results of inhibition of the programmed cell death is increased longevity and accumulation of B cells. This represents, certainly, a new staging study to fully evaluate the disease before and after treatment and may be a new way to understand if LD-TBI induces, directly or indirectly, apoptosis.

These results incite us to prove the impact of this treatment on long-term disease-free survival in such patients, and to start the EORTC Lymphoma Group, a randomized clinical trial comparing IF-RT vs. LD-TBI + IF-RT. In addition, molecular biology studies will help us to understand how LD-TBI works (direct and/or indirect induction of apoptosis; relationship with t(14;18) translocation, and overexpression of bcl-2), and to predict the evolution of the disease through the detection of t(14;18)-bearing cibles with polymerase chain reaction (PCR).

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