Is there any place for a wait-and-see policy in stage I\textsubscript{0} follicular lymphoma? \\ A study of 43 consecutive patients in a single center

P. Soubeyran, H. Eghbali, M. Trojani, F. Bonichon, P. Richaud & B. Hcerni
Institut Bergonie, Regional Cancer Center, Bordeaux, France

Summary

Background: A wait-and-see policy (WS) does not appear to modify the long-term prognosis of advanced-stage follicular lymphomas (FL), while irradiation of limited stages sometimes causes complications and does not avert distant relapses. Consequently, we decided to test WS in a selected subset of the localized FL, i.e., patients in complete remission (CR) after the initial lymph node biopsy (stage I\textsubscript{0}).

Patients and methods: Forty-three previously untreated patients were diagnosed with stage I\textsubscript{0} FL and 26 of them were included in the WS. Their median age was 60.3 years; 19 were male and 24 female. All histological slides were reviewed and confirmed the diagnosis of FL. Median follow-up was 6.3 years (y).

Results: Thirteen of the 26 untreated patients are still relapse-free, while six relapsed locally only (median: 4.2 years after diagnosis), and reattained CR with radiotherapy. Seven patients relapsed at distant sites (median: 1 year after diagnosis). No localized relapses were observed in the treated group, but there were 7 distant relapses.

Conclusions: The use of WS in stage I\textsubscript{0} FL did not appear to modify the prognosis of these patients. Furthermore, we observed two distinct patterns of relapse (local and distant) that are difficult to differentiate at onset.

Key words: follicular lymphoma, limited stages, wait-and-see policy

Introduction

Many aspects of follicular lymphoma (FL) make it a rather peculiar disease. Indolent clinical course, dissemination, frequent relapses and long survival are its main features, and Jaffe even wondered whether in fact it is a malignant tumor [1]. Finally, prediction of its evolution remains difficult [2].

Involved-field radiotherapy remains the treatment of choice for localized FL, since up to 50% of patients thus treated are still disease-free at 10 years, with a low relapse rate thereafter [3–6]. Radiotherapy, however, requires at least 4 weeks and is associated with minor but frequent discomfort such as cutaneous erythema, diarrhea for abdominal volumes and mucositis for cervical and Waldeyer ring irradiation. Furthermore, in a limited subset of patients, it can lead to complications such as xerostomia in patients with Waldeyer ring irradiation (particularly the elderly) or limb œdema for inguinal and iliac localization (depending on the extent of initial tumor burden and diagnostic surgery). On the other hand, a wait-and-see policy (WS) does not appear to modify the long-term prognosis of the advanced stages of FL [7–9], with frequent observations of spontaneous tumour regression.

Finally, the usefulness of involved-field radiotherapy could be weighed against the risk of induced complications in patients with no residual tumor following the initial diagnostic surgery (stage I\textsubscript{0}) which can be locally controlled without additional irradiation. Do we have to treat these patients when the expected local relapse rate may be low, while the expected complication rate may be high?

In an attempt to answer this question, we conducted a prospective study to evaluate a wait-and-see approach for stage I\textsubscript{0} FL.

Patients and methods

From 1984 to 1995, 43 previously untreated patients with stage I\textsubscript{0} FL were followed at the Institut Bergonie. Histological diagnoses were reviewed at the time of diagnosis and recently confirmed in all cases by one pathologist (MT): they were classified as centroblastic-centrocytic, either follicular (34 cases, 79%) or follicular and diffuse (9 cases, 21%) according to the Kiel classification [10], and as either B (12 cases, 28%) or C type (31 cases, 72%) according to the Working Formulation [11].

Pretreatment clinical work-up was performed as usual and included lymphangiography in 9 patients (21%), abdominal CT scan in 28 patients (65%) and both in 6 patients (14%). Unilateral bone marrow biopsy was not systematically performed (22 patients, 51%) in the early years since the probability of bone marrow involvement was expected to be low and probably minimal in patients with only one involved site [12]. Furthermore, this would not have changed treatment strategy while considering the absence of cure of disseminated disease with chemotherapy in FL and the uncertain prognostic impact of such a low and rare bone marrow involvement.

Patient characteristics are outlined in Tables 1 and 2. Extranodal sites included parotid (2 cases) and tonsil (1 case). LDH evaluation was performed from 1988: one of 21 patients presented LDH elevation.
Inclusion in the WS was restricted to patients who could be thoroughly followed up and in whom there was no suspicion of residual disease. Consequently, 17 case (40%) were excluded either for the above reasons (localization either inguinal or axilla (6 cases, 14%), doubtful scar tissue (2 cases, 5%), psychiatric disease (1 case, 2.5%) or simultaneous cancer (1 case, 2.5%), in accord with patient wish (5 cases, 12%) or because of intermediate grade before pathology review (2 cases, 5%). Finally, 26 patients were included in the WS.

### Treatment procedures

Involved-field irradiation up to 40 Gy (20 fractions, 4 weeks) was performed in all 17 of the patients treated. In addition to radiation, three patients received induction chemotherapy with the CVP combination (cyclophosphamide, vincristine and prednisone) [13].

### Evaluation and follow-up procedures

All patients were in complete remission (CR) following diagnostic surgery. At relapse, restaging was performed by the same guidelines: abdominal CT scan in 14 patients, lymphangiography in 4 patients and both in 2 cases, and unilateral bone marrow biopsy in 7 of 20 patients. In instances of relapse, treatment response was evaluated as usual: CR represented the disappearance of all signs and symptoms of disease as determined by clinical and radiographic evaluation. The remaining patients were considered non-responders.

Patients were then followed quarterly for 3 years, twice a year for the next 2 years and then annually. Follow-up procedures included clinical examination, chest X-ray, complete blood cell counts and appropriate radiographs when indicated. None of the patients were lost to follow-up.

### Statistical analysis

We followed the recommendations of Dixon [14], who proposed a standardised reporting of outcome. Survival was computed from date of pathology diagnosis. For overall survival (OS), all causes of death were considered as events. Time to treatment failure (TTF) was measured from date of pathological diagnosis until date of relapse, disease progression, death due to treatment, or withdrawal. Patients without any event were considered as censored data at the date last known to be alive. Relapse, progression, treatment-related deaths and withdrawals were considered as events. Relapse was considered as from the appearance of the first symptom. Time to relapse (TTR) was computed from the date of pathology diagnosis until relapse or date last known to have been free of disease, counting only relapses as events.

Survival curves were computed by the Kaplan-Meier method. For the population as a whole, 95% confidence intervals are represented, and the number of patients at risk at 3, 5 and 7 years is shown in the remaining figures.

The cut-off date for the current analysis was January 30, 1996. The median follow-up was 6.3 years (y) (range: 0.3 and 11.6 y) for the population as a whole, 8.2 y for the WS group (range: 1 to 11.6 y) and 5.4 y for the treated group (range: 0.3 to 8.4 y).

### Results

#### Overall survival

At the time of analysis, 34 patients were alive, including 31 with no evidence of disease and 3 with disease; 9 patients had died, 5 of FL and 4 of other causes. Five- and 7-year OS were 82.5% and 74.5%, respectively (Figure 1).

In the WS group (26 patients), 19 patients were alive, 17 of them without evidence of disease and 2 with disease; 7 patients had died, 4 of them of lymphoma. Five- and 7-year OS were 82.5% and 69%, respectively (Figure 2).

In the treated group, 15 patients were alive, including 14 without evidence of disease and one with disease; 2 patients had died, one of them of lymphoma. Five- and 7-year OS were both 84.5% (Figure 3).

#### Relapse

All of these patients were in CR before any treatment (stage I), and 20 of them relapsed. Five- and 7-year TTR were 53% and 42.5%, respectively (Figure 1). Of the patients in the WS group (Table 2), 13 have as yet not relapsed (median F/U: 4.6 y; range: 0.8 to 11 y). Six patients relapsed exclusively in the initially involved site (localized relapses) 0.6 to 9 y after diagnosis (median: 4.2 y). One patient is currently not in treatment because of age and a slowly-growing tumor (Patient # 13 – Table 2). The five remaining patients were treated by radiotherapy and again achieved CR: one of them died of subsequent relapse (#25 – Table 2); one
Table 2. Untreated patients. Description of disease and outcome.

<table>
<thead>
<tr>
<th>Gender</th>
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<th>Staging</th>
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</table>

List of abbreviations: Pathol — pathology (Working Formulation); BMB — bone marrow biopsy; TTR — time to relapse i.e., delay from diagnosis to relapse; M — male; F — female; L — left; R — right; sclv — supraclavicular nodes; axil — axillary nodes; parot — parotid; ing — inguinal nodes; lymphog. — lymphoangiogram; CT scan — CT scan of the abdomen and pelvis; inv site — initially involved site; LA — latero-aortic nodes; BM — bone marrow; NED — no evidence of disease; IC — intercurrent disease; m. — months.

Figure 1. Whole population (43 patients). Overall survival and time to relapse. Ninety-five percent confidence intervals are outlined.

Figure 2. WS group (26 patients). Overall survival and time to relapse. Number of patients at risk at 3, 5 and 7 years are outlined.
reached twice thereafter (always in contiguous areas, i.e., right axilla, then right supraventricular, then mediastinum), achieving CR again with combined chemotherapy and radiotherapy (#4 – Table 2), but later dying of intercurrent disease; 3 patients are alive with no evidence of disease (1.3 to 10 y of follow-up).

Seven patients relapsed outside the initially involved area 0.5 to 5.5 y after diagnosis (median: 1 y). The relapses were localized in 4 patients (#11, 12, 16, 26) and disseminated in 3 (#17, 19, 20), with 4 showing histological transformation (#12, 16, 17, 20) (5 lymph node biopsies and 2 lymph node aspirations). Four relapses responded to salvage treatment, achieving CR again, while 3 failed to respond (all of these cases were transformed, and died within a year). Five- and 7-year TTR of the 26 patients were 56% and 41%, respectively (Figure 2).

Ten of the 17 patients treated remained relapse-free. None of the seven relapses, three of them stage I, one stage II, two stage III and one stage IV (the only one with LDH elevation), occurred in the initially involved (and irradiated) areas. Histological transformation to diffuse centroblastic-centrocytic occurred in one of six cases (4 lymph node biopsies and 2 lymph node aspirations). The treatment of the relapses depended upon disease extent, including involved field irradiation in the four localized relapses and in one limited stage III [15] and chemotherapy in the three advanced stages and in one localized case (the one that was histologically transformed). Five of these relapsed patients achieved CR, while two failed to respond to treatment (one stage I, which ultimately transformed into a centroblastic type, and the stage IV with LDH elevation). Five- and 7-year TTR were 43.5% (Figure 3).

Discussion

Although not frequent, stage I, FL is also not rare and warrants attention. During a 12-year period, we recruited 43 of these patients, which may be considered a large series with good follow-up (6.3 years median). Sixty percent of them were included in the WS. Anticipated reasons for excluding patients from the WS group were dubious scar tissue, difficult follow-up for various reasons (disease location such as inguinal nodes that could spread indolently in the abdomen, age, patient domicile too far from the Center) or risk of complications following irradiation (xerostomia following Waldeyer ring irradiation, limb oedema following inguino-iliac radiotherapy). We subsequently encountered additional reasons: patient reluctance to agree to WS (5 cases, 12% of the patients) and histological problems (2 cases, 5%). Ultimately, the principal ones were disease localization (because of follow-up difficulties or risk of complications) and patient choice.

Patient features were in accord with expectation: 60 years median age, good performance status, absence of B-symptoms, normal LDH values in most of the cases [16]. The adverse outcome of the only patient with LDH elevation should be noted.

Our results confirmed the hypothesis that radiotherapy could be avoided in some patients with stage I, FL. Indeed, among the 26 patients included in the WS (8.2 years median follow-up), we encountered three types of outcome: no relapse, relapse localized in the initially involved area (localized relapse) and distant relapse. WS averted useless and possibly harmful irradiation for the seven patients who had distant relapses and the 13 patients who have not relapsed as of the present, i.e., 20 out of 26 patients.

Six out of 26 patients had localized relapses, and all six were in the WS group. Most of these relapses were treated with radiotherapy and the patients reached CR; three of them are still free of disease. There is no evidence that earlier irradiation would have changed the outcome. However, it could be argued that these patients have suffered relapse and consequently psychological injury that could have been avoided with appropriate treatment.

The long delay of up to nine years (median 4.2 years) from diagnosis to localized relapse that we observed is surprising and argues for a tendency for these particular patients to progress locally as well as slowly [17]. Five of these six relapses confirm this impression, particularly the one that occurred successively in three contiguous areas, where it was easily controlled by radiotherapy with or without chemotherapy. Only one of the patients had a further distant relapse of which he died.

Most of the distant relapses occurred soon after diagnosis (median 1 year). These evolutions argue for a propensity for dissemination as well as higher doubling time. The frequency of histological transformation (4 out of 7 patients) is in accordance with this latter hypothesis. However, none of the known characteristics of the patients, including pathology features, was predictive of this outcome. Further research on prognostic factors should probably focus on this problem.

There were no local relapses in the treated group. We encountered the predictable, that is, a high rate of
complete local control with radiotherapy in the initially involved field, and OS and TTR in accord with those in the literature [4, 5, 18]. Nothing particularly noteworthy has been observed.

Finally, as of now 14 distant relapses have been observed, showing the propensity for dissemination in a significant fraction of these patients. Paradoxically, this observation would argue for systemic rather than local treatment. However, chemotherapy demonstrated no survival advantage in previous randomized studies [19–21]. Interferon-α would be another good candidate for such a systemic treatment [22], but its tolerance precludes its use in limited disease. Furthermore, a recent trial failed to demonstrate any survival advantage in low-tumor-burden FL [23]. Low-dose total-body irradiation may be a good candidate, since the procedure is brief and well tolerated [24, 25].

Although retrospective studies have demonstrated long-term freedom from disease in almost half the localized FL with involved-field irradiation [3–6], no randomized trial assessing this treatment in comparison to WS has been conducted. Our results argue for the WS in the treatment of stage I_0 FL, but only a randomized trial could definitely confirm this. It would probably be illusory to consider conducting such a trial in this small and infrequent subset of FL. A more realistic objective might be to concentrate first on disseminated diseases which occur more often, since the benefits of any progress in those will subsequently also accrue to localized diseases.

Finally, this series has enhanced our knowledge of the natural history of follicular lymphomas. We observed varied outcomes with FL; some appeared to evolve locally and others had an apparent propensity to disseminate, and only follow-up appeared capable of defining which was which. The ability to discriminate between the two groups of patients would help to determine the ones with the potential to benefit from systemic treatments and, further, to design trials that could answer the question. The only hope we currently have is to improve our knowledge of residual disease. Comprehension of its kinetics would be crucial and, fortunately, is possible through the detection of t(14;18)-bearing cells with polymerase chain reaction (PCR). Although increasing, our knowledge is still limited [26, 27]. We have the capability to detect [28, 29] and to quantify the circulating cells [30], and also to evaluate the functional status of hybrid bcl-2 in these circulating cells [31]. Preliminary results are still conflicting [32–35] and as a result, clinicians are not as optimistic as they are about other hematologic malignancies [36]. Yet, currently published studies are retrospective and either concern too few patients or use different methods: the predictive value of this new tool cannot currently be assessed without a prospective multicentric study with PCR quality control.

Localized stages certainly are the best choice for such a study since they include possibly cured patients as well as many others who will ultimately relapse [3–6]. The problem of relapse prediction is not so important in advanced stages since it is known that most of them, if not all, will ultimately relapse, the only question being how long it will take [37]. The problem would change should a curative treatment for disseminated follicular lymphomas become available; recently published results extend this hope [22].

References


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Correspondence to:
Pierre Soubeyran, MD
Institut Bergonie, Regional Cancer Center
180, rue de Saint-Genès
33076 Bordeaux Cedex, France