High Molecular Response Rate and Clinical Correlation in Patients with Follicular Lymphoma Treated with Cyclophosphamide-Vincristine-Prednisone plus Interferon α 2b

Elena Fernández-Ruiz, María Cabrerizo, Mara Ortega, Carlos Blas, Pilar Llamas, Matilde Santos-Roncero, Santiago Nieto, Agustín Acevedo, Guillermo Pérez, Concepción Nicolás, José María Fernández-Raia, and Reyes Arranz

ABSTRACT

Purpose: The role of molecular monitoring of minimal residual disease (MRD) in low-grade non-Hodgkin’s lymphoma is controversial. We have performed a prospective study of the molecular behavior of 35 patients with follicular lymphoma who received cyclophosphamide-vincristine-prednisone chemotherapy in conjunction with IFN-α 2b.

Experimental Design: Bcl-2 and clonal immunoglobulin heavy chain (IgH) gene rearrangements were assayed at diagnosis by PCR in lymph node and bone marrow (BM) and sequentially after treatment.

Results: Molecular markers were detected in BM of 29 (83%) patients at diagnosis: Bcl-2 rearrangement in 20 patients (90% major breakpoint and 10% minor cluster) and clonal IgH rearrangement in 9 of 15 patients negative for Bcl-2. Molecular and clinical response was noted in 25 (86%) patients after induction treatment. Progression-free survival at 5 years was 78.1 ± 8%. A correlation between clinical and molecular response was found in 24 patients with molecular markers in BM at diagnosis and >2 years of follow-up: 94% of patients with undetectable MRD showed continuous clinical remission, whereas 50% of patients who reverted back to positive molecular markers relapsed (P < 0.05).

Conclusions: The rate of molecular response is high in patients treated with cyclophosphamide-vincristine-prednisone and IFN and MRD sequential analysis is useful for disease surveillance.

INTRODUCTION

Currently, there is no standardized first line treatment for low-grade NHLs, and they are generally assumed to be incurable. Although a high rate of remission can be achieved, the usual outcome is characterized by continuous relapses with a progressive more refractory disease (1). On the other hand, the assessment of the impact on survival of any treatment is hindered by the occurrence of nondisease-related deaths because of the advanced age of the affected population and because a prolonged observational period is required before any conclusion can be made. However, it has been reported that recombinant IFN, purine analogues, and high-dose chemotherapy can significantly extend remission duration (2–6). Although a significant improvement in the survival rate has seldom been proven, results seem to compare favorably with historical data, and it is likely that better outcomes will be detected with longer follow-up.

The majority of patients with follicular NHL has identifiable molecular markers, which provide a valuable tool for detecting MRD and, therefore, the quality of the clinical response. t(14;18)(q23;q21) translocation characterizes FLs and results in Bcl-2 oncogene rearrangement with a deregulated expression of Bcl-2 protein (7, 8). This rearrangement is detected by PCR in 60–85% of patients with FL (9). The t(14;18) breakpoints on chromosome 18 that disrupt the Bcl-2 gene are known as the MBR and the mcr regions (10–12). In the subset of patients with FL without detectable Bcl-2 rearrangement, tumor clonality can be assessed by PCR-based amplification of the CDRs 2 or 3 of the immunoglobulin heavy chain (IgH) gene (13, 14).

Nowadays, the clinical significance of an undetectable MRD is the focus of much research (15). Its association with a more prolonged remission has been demonstrated mainly in patients with relapsed or refractory NHL of low and intermediate grade treated with high-dose chemotherapy or radiotherapy.

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and hematopoietic stem cell support (16–20). Studies performed in patients treated with standard dose chemotherapies have yielded more controversial results. Lambrechts et al. (21) and Price et al. (22) detected MRD in patients with prolonged clinical remissions. However, in those studies, the number of patients analyzed was small or serial determinations were lacking. In contrast, a significantly higher survival rate has been demonstrated in patients with FL who achieved a molecular response when compared with nonresponders (76 versus 38%; Ref. 23). Molecular responses have also been reported in patients with relapsed NHL receiving more novel treatments such as an anti-CD20 chimerical antibody (24, 25) or anti-idiotypic vaccines (26), although their clinical significance remains to be determined. Mandigers et al. (27) have recently questioned the significance of the molecular response because they did not find any correlation between the molecular status assessed by real-time PCR and the clinical response in patients with FL treated with CVP and IFN-α 2b.

Most of the recent studies dealing with treatment efficacy in patients with FL include molecular results, although the clinical importance of molecular monitoring is yet to be confirmed. We previously reported a significantly prolonged PFS in patients treated with CVP in conjunction with IFN when compared with patients treated solely with CVP (2). Here, we present a molecular prospective study, performed in 35 patients consecutively treated with this combination. The association between an undetectable MRD and the clinical outcome is also analyzed.

**PATIENTS AND METHODS**

**Patients and Clinical Evaluation.** On the basis of our previous observations (2), our current induction treatment policy for patients older than 18 years, with stage II–IV follicular NHL, is CVP plus IFN-α 2b. Grade 3 FLs are excluded. Consent to obtain serial BM samples was required. At diagnosis, all patients were staged, including hemogram, biochemistry, serum lactate dehydrogenase levels, cervical-thoracic-abdominal and pelvic computed tomographic scans, and bilateral BM biopsies. Obtaining serial BM samples was required. At diagnosis, all patients were staged, including hemogram, biochemistry, serum lactate dehydrogenase levels, cervical-thoracic-abdominal and pelvic computed tomographic scans, and bilateral BM biopsies.

**Treatment.** The treatment schedule has been described previously (2). To summarize, all patients received CVP (oral cyclophosphamide (2000 mg/m²), i.v. vincristine (1.4 mg/m²), and oral prednisone (100 mg/m²)) every 21 days. s.c. IFN-α 2b at a dose of 3 MU/m² was simultaneously administered three times/week for 3 months. The number of cycles of chemotherapy administered was those necessary to achieve CR or maximum response, defined as an unchanged partial response after two or three additional cycles. Growth factors were administered if grades 3–4 granulocytopenia developed, and radiotherapy was delivered on sites of previous bulky disease (>7 cm) or suspected residual mass. After induction therapy with CVP and IFN, 10 patients received maintenance IFN-α 2b.

**Follow-Up and Clinical and Molecular Response Criteria.** Patients were evaluated 1 month after induction therapy, then every 4–6 months for the first 2 years and twice a year thereafter, with repeated laboratory tests and complete restaging, including BM biopsies. In patients in stages II and III and without evidence of recurrence, BM biopsies were performed at longer intervals. CR was defined as the disappearance of any evidence of disease with normal BM 1 month after completion of treatment. PR was defined as a reduction of at least 50% in tumor mass, with no increase of preexisting lesions nor the appearance of new ones. No response was defined as any response less than a partial response. Molecular response was defined as the disappearance of the molecular marker in BM after treatment, assessed using PCR analysis.

**Genomic DNA Isolation.** Mononuclear cells were isolated from BM aspirates by Ficoll/Hypaque gradient centrifugation (Lymphoprep; Nycomed Pharma, Nyeegaard, Norway) and washed twice in PBS. Genomic DNA was purified using the single tube DNA isolation kit (Biotec Laboratories, Houston, TX) as recommended by the manufacturer. DNA was resuspended in distilled water after isopropanol precipitation and stored in aliquots at −20°C. With respect to the LN biopsies, tissue samples from 7 patients were frozen and genomic DNA obtained as described above. The rest of the LN samples (20) were only available as paraffin-embedded biopsies. Sections were dewaxed twice in xylol for 5 min and rehydrated through a series of ethanol dilutions. Genomic DNA was then isolated using a proteinase K-based kit as recommended by the manufacturer (Lymphoma B diagnostic kit; Master Diagnostica). Genomic DNA concentration was determined by measuring its absorbance at 260 nm. Amplification was performed for the human DCIR gene so as to demonstrate amplifiable DNA.

**PCR Analysis.** Serial PCR sample analysis was carried out as follows: before treatment in LN and BM; at 3–5, 6–8, and 9–12 months in BM during the first year; and every 6 months thereafter. Bcl-2 and monoclonal IgH rearrangement amplifications were successively performed. BM aspirates were used for molecular follow-up monitoring as detection of Bcl-2 at diagnosis was more frequent in these samples than in PB. In fact, we performed both determinations in 16 patients and observed that 50% of the patients presented Bcl-2-positive results in BM while testing negative in PB. Regarding IgH rearrangements, false-negative results were reduced by the study of both CDR2 and CDR3 regions. Appropriate negative and positive controls were included in each PCR. Samples were tested independently by two researchers, and 90% concordance was obtained in every case. Level of sensitivity was determined using serial dilutions of different cell lines in normal PB mononuclear cells. For Bcl-2 and CDR3 IgH rearrangements, the Karpas 422 lymphoma cell line was used (kindly provided by Dr. Miguel Angel Piris, Centro Nacional de Investigaciones Oncológicas, Instituto de Salud Carlos III, Madrid, Spain). One tumor cell in 10⁶ normal cells provided positive results. For the CDR2 IgH rearrangement, the sensitivity given by the manufacturer was one tumoral cell in 10⁵ normal cells.

**Detection of Bcl-2 and IgH Rearrangements.** Nested PCR with specific oligonucleotides for the major (MBR) and minor (mcr) breakpoint regions was performed as previously described by Gribben et al. (28). Briefly, each PCR assay was performed for 25 cycles (1 min at 94°C, 1 min at 55°C, and 1 min at 72°C). Nested PCR was performed using 5 μl of the first PCR product for 30 cycles with an annealing temperature of 58°C. PCR products were analyzed on ethidium bromide-stained 2.5% agarose gels. For the detection of IgH rearrangement, two different PCR assays were carried out so as to amplify the junctional areas of the VDJ region. CDR3 was amplified by...
a single round of PCR as described previously (14). PCR was performed for 35 cycles (45 s at 94°C, 45 s at 55°C, and 45 s at 72°C). For CDR2 amplification, a seminested PCR method was used (Lymphoma B diagnostic kit; Master Diagnostica) as recommended by the manufacturer. Both CDR3- and CDR2-amplified products obtained were denaturated at 95°C for 10 min and subsequently maintained at room temperature to induce duplex DNA formation. They were then analyzed by electrophoresis in 10 and 6% polyacrilamide (19/1) gels, respectively, and stained with ethidium bromide.

DNA Sequence Analysis. To confirm that PCR products corresponded with real translocations, the amplified bands from 4 patients (3 with Bcl-2 and 1 with IgH rearrangements) were cloned using the Topo-TA cloning kit (Invitrogen, Carlsbad, CA), and five clones from each sample were sequenced using the D-rhodamine terminator cycle sequencing kit and an ABI Prism 337 DNA sequencer (Perkin-Elmer-Applied Biosystems, Foster City, CA). The sequences obtained were submitted to the GenBank database (accession nos.: AF487993 and AF487995 for MBR, AF487996 for mcr, and AF487991 for CDR2).

Table 1 Patient’s characteristics

<table>
<thead>
<tr>
<th>a. Clinical data</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>35</td>
</tr>
<tr>
<td>Age (median, range)</td>
<td>57 (26–79 years)</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>14/21</td>
</tr>
<tr>
<td>Ann Arbor stage</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>5</td>
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<tr>
<td>III–IV</td>
<td>30</td>
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<tr>
<td>IPFI</td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>19</td>
</tr>
<tr>
<td>≥2</td>
<td>16</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>b. Molecular data</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Histological BM infiltration (n = 26)</td>
<td></td>
</tr>
<tr>
<td>Bcl-2 (+)</td>
<td>15 (58%)</td>
</tr>
<tr>
<td>IgH rearrangement (+)</td>
<td>8 (31%)</td>
</tr>
<tr>
<td>Undetectable molecular marker</td>
<td>3 (11%)</td>
</tr>
<tr>
<td>Histological BM not infiltrated (n = 9)</td>
<td></td>
</tr>
<tr>
<td>Bcl-2 (+)</td>
<td>5 (56%)</td>
</tr>
<tr>
<td>IgH rearrangement (+)</td>
<td>1 (11%)</td>
</tr>
<tr>
<td>Undetectable molecular marker</td>
<td>3 (33%)</td>
</tr>
</tbody>
</table>

Molecular Markers in BM Aspirates and LN at Diagnosis. Genomic DNA from BM aspirates and LN tissue sections were subjected to Bcl-2 and IgH rearrangement amplification by PCR. Twenty of 35 (57%) patients had Bcl-2 rearrangement in BM aspirates. The translocation at MBR was detected in all but 2 (18 of 20, 90%) patients, who presented the mcr breakpoint. Bcl-2 rearrangement was not detected in 15 (43%) patients, whereas 9 of these showed monoclonal IgH rearrangements. In 6 (17%) patients, no molecular marker could be detected in BM. To summarize, the majority of patients (29 of 35, 83%) had detectable molecular markers in BM at diagnosis (Table 1b). Molecular analysis was performed in LN tissue sections from 27 (77%) of 35 patients included in the study, and molecular markers were detected in 23 (data not shown). Discordant results were observed in 3 patients (13%) who tested positive for IgH rearrangement in LN while showing positive for Bcl-2 in BM. Finally, we did not detect any molecular marker in LN tissue sections from 4 patients. Two did not have molecular markers in BM and 2 showed Bcl-2 rearrangements. The findings in these latter cases could be because of the low DNA quality of the LN paraffin-embedded tissue.

Table 2 Therapy and clinical response of the patients

| No. of patients | 35 |
| Treatment (CVP + IFN) |  |
| No. of cycles (median, range) | 8 (5–11) |
| Maintenance IFN |  |
| Yes | 10 |
| No | 25 |
| Time between diagnosis and treatment (median, range) | 33 (15–110 days) |
| Clinical response after treatment induction |  |
| Complete | 28 (80%) |
| Partial | 6 (17%) |
| Progressive disease | 1 (3%) |
| PFS |  |
| At 2 years | 90.5 ± 5% [95% (CI) 80.2–100%] |
| At 5 years | 78.1 ± 8% [95% (CI) 62.3–93.9] |
| Follow-up (median, range) | 37 (13–59 months) |

RESULTS

Patient’s Characteristics. Forty-four patients were diagnostosed since February 1997. Nine were excluded from this study because of the following reasons: 2 patients refused sequential marrow aspirations; 1 patient had grade 3 FL; 5 patients had a marginal zone lymphoma; and 1 elderly patient with small lymphocytic lymphoma but without symptoms. Characteristics of the 35 patients with grade 1 or 2 FL included in the study are summarized in Table 1a.

Clinical Response. After receiving CVP+IFN-α 2b induction treatment (Table 2), 80% of the patients achieved CR. PR was observed in 17% of patients: two of these later showed a complete response because a gradual disappearance of LN enlargement on computer-assisted tomography scans was observed during the follow-up, whereas another 2 showed no additional progression at 31 and 30 months, respectively. Two patients with PR and 3 with CR (5 of 35, 14%) had progression by the end of the study. Two patients died because of refractory disease in one case and transformation in the other.

Follow-Up of Molecular Markers and Clinical Response. Molecular markers and clinical outcome are summarized in Fig. 1. We considered positive those patients with at least one molecular marker in BM, detected at diagnosis by PCR. Of those cases which were positive for Bcl-2 and IgH rearrangements, only the former are shown because of the higher sensitivity reached by nested PCR. In 3 cases with LN IgH positive and BM Bcl-2 positive, both markers are shown. Twenty-five (86%) of 29 patients with positive molecular markers achieved molecular response after induction treatment with
CVP+IFN: 24 patients within a year of diagnosis; 20 patients with clinical CR; and 5 patients with PR. Four of these 5 patients with clinical PR maintained molecular remission and have not progressed: 2 attained a clinical CR on additional follow-up and 2 remain in long-lasting PR. The fifth repopulated and progressed. One patient with persistent positive markers (UPN 33) suffered progressive disease. In 3 patients, samples were available after this period: 2 patients achieved molecular response and clinical CR and 1 patient without molecular response progressed after a short PR (UPN 32). We did not observe any effect provoked by maintenance IFN in the molecular response of the 8 patients with molecular markers at diagnosis because at the time of administration they were yet molecular responders.

Twenty-seven (77%) of 35 patients underwent >2 years of follow-up, 24 having shown positive markers in BM at diagnosis. The correlation between clinical and molecular response is shown in Table 3. Fifteen (94%) of 16 patients showed a continuous undetectable MRD status and remained in clinical CR, whereas 4 (50%) of 8 patients tested positive in the last follow-up, although they remained in CR. Four patients with detectable MRD over time (P < 0.05) showed clinical evidence of relapse or progressive disease, and 1 patient without detectable MRD suffered a local extramedullary relapse (UPN 23). The median number of samples analyzed during the monitoring of MRD was 7 (range, 4–13) for PCR-negative patients and 7 (range, 4–10) for PCR-positive patients. Insofar as the effect of maintenance IFN in molecular relapse, 1 of 8 (12%) patients who received it and 6 of 15 (40%) patients who did not receive it reverted back to positive molecular markers, although the difference is not statistically significant (data not shown).

All of the patients that reverted to positive PCR showed identical molecular patterns at onset and relapse, and in the 2...
cases analyzed (1 MBR and 1 CDR2), sequences were identical (GenBank accession nos. AF487993 and AF487994 and AF487991 and AF487992).

**DISCUSSION**

The aim of this study was to assess the molecular response in patients with FL treated with CVP in conjunction with IFN-α 2b and to test the relationship of the molecular findings with their clinical evolution.

With regard to the molecular results at diagnosis, there are two aspects that we would like to point out: the source of samples required to perform the molecular monitoring and the percentage of *Bcl-2* negativity detected. In this study, we have found that the detection of molecular markers (*Bcl-2* and *IgH* rearrangements) is better in BM than in PB. These results are similar to those recently reported for *Bcl-2* rearrangement by Colombat *et al.* (29) and Rambaldi *et al.* (30), whose first-line therapy consisted of rituximab alone and with cyclophosphamide-Adriamycin-vincristine-prednisone, respectively. In accordance with our findings, Gribben *et al.* (31) also reported that BM is a more informative sample in relapsed patients treated with high-dose therapy and stem cell support. In contrast, other authors have found concordance between PB and BM findings (23, 32, 33). The discrepancy in these findings should be resolved as the results, and the assessment of treatment efficacy may change significantly. Moreover, the source of samples is important because it has a bearing on the patient’s comfort during the prolonged follow-up required.

On the other hand, *Bcl-2* rearrangements were detected in 60% of the patients in at least one of the analyzed tissues. This incidence is similar to that reported in other European series (34, 35) but differs from the 82% positivity detected in studies performed in the United States (32, 36). Fortunately, monoclonal *IgH* rearrangements were detected by us in 34% of *Bcl-2*-negative patients, thereby reducing the risk of losing patients suitable for molecular monitoring. In fact, only 2 of 35 (6%) patients tested negative for any molecular marker, both in BM and LN. In conclusion, we have found that the combined use of *Bcl-2* and *IgH* rearrangements provide a molecular marker at diagnosis for 94% of the patients. A possible criticism of the usefulness of *IgH* clonality for MRD detection is its lower sensitivity when compared with that of nested PCR for *Bcl-2* detection. *IgH* rearrangements have a lower sensitivity because clonal DNA-specific amplification takes place within a polyclonal *IgH* rearranged B-cell population. However, its sensitivity is still greater than conventional flow cytometry and cytological or immunohistochemistry techniques. Furthermore, in our series, persistent *IgH* PCR negativity is associated with long-term clinical remission, and therefore, we did not have to discard the 40% of patients who showed negative for *Bcl-2* rearrangement. Additional studies are required to increase the sensitivity of *IgH* PCR assays, likely to be made possible through the development of patient-specific primers and probes (14, 18).

We found the same molecular markers in LN and BM in 80% of the patients studied. In fact, in three cases analyzed (two MBR and one mcr), the sequences were identical. The 5 (20%) discordant cases were negative for *Bcl-2* rearrangement in LN while being positive in BM. López-Guillermo *et al.* (32) reported a lower incidence of discordance (5.8%), but although they worked with fresh specimens, we used mostly paraffin-embedded tissue sections. Hoeve *et al.* (37) also reported a higher correlation using frozen samples. However, in 3 of 5 discordant cases in our study, LN was positive for *IgH* rearrangement, whereas BM was negative. Therefore, it is feasible that the *Bcl-2* rearranged cells detected in these cases correspond with nonmalignant cells (38, 39) and that the malignant cell clone only accounts for the *IgH* rearrangement. Thus, 1 of these patients (UPN 18), despite reverted back to being *Bcl-2* positive, remained *IgH* negative and continues to be in CR. This slightly puzzling finding will be clarified if, when in the event that this patient relapses, the specific tumor molecular marker reappears.

Among the patients studied, molecular response correlated with clinical response. Loss of molecular marker correlated with clinical CR in 76% of the patients. In addition, 80% of the patients with PR and molecular remission have not progressed thus far. Therefore, the achievement of a molecular response seems to correlate better with disease outcome. Recently, Mandigers *et al.* (27) questioned the usefulness of the molecular response in patients with FL treated with eight cycles of CVP in conjunction with IFN-α 2b. Using real-time PCR in PB samples before and after the induction treatment, they found a sharp diminution in the number of circulating *Bcl-2*-positive cells, irrespective of the clinical response. This study was performed solely in PB samples, whereas BM cells could still have been positive at the time of analysis. This fact could account for the discrepancy with the results described here.

Once MRD is undetectable, sequential monitoring of MRD could be used as a surrogate marker for disease outcome. López-Guillermo *et al.* (23) found a significant association between the molecular behavior pattern and PFS. Time to progression was significantly longer for patients achieving molecular response, and persistence of undetectable MRD than that for both those patients who were PCR negative after treatment but with detectable MDR during the follow-up and those patients without molecular response. We cannot perform the same analysis because of the few patients and the low incidence of events to the present date. However, for the group of patients with prolonged follow-up, the presence of detectable MRD is associated with evidence of clinical relapse or disease progression. In our series, 94% of patients who maintained the molecular response were in continuous clinical remission, whereas 50% of the patients who lost the molecular response had a clinical relapse (*P* < 0.05).

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**Table 3** Correlation between clinical and molecular findings in 24 patients with positive markers found in BM at diagnosis and observed for >2 years".

<table>
<thead>
<tr>
<th>Clinical response (%) Relapse/Prog (%)</th>
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<tr>
<td>PCR− (n = 16) 15 (94%) 1 (6%)</td>
</tr>
<tr>
<td>PCR+ (n = 8) 4a (50%) 4 (50%)</td>
</tr>
</tbody>
</table>

a *p* < 0.05; S, (sensitivity): 79%; E, (specificity): 80%; PPV, (positive predictive value): 94%; NPV, (negative predictive value): 50%.

Three patients became once positive in the last follow-up, and 1 patient fluctuated between negative and positive results.
The role of IFN in the treatment of low-grade NHL has been largely studied in prospective random trials carried out as a part of the induction treatment or as consolidation for responding patients (2–5). In our study, PFS advantage was observed in patients receiving IFN as part of the induction treatment, regardless of the maintenance IFN received. The majority of studies have demonstrated a significantly prolonged remission duration when compared with that of standard chemotherapy. Unfortunately, the molecular response was not assessed in these studies. Our data suggest that the addition of IFN to the standard induction chemotherapy results in a high rate of molecular responses, similar to that observed with combinations of third generation treatments or fludarabine-based regimens (23).

In summary, a high rate of molecular response can be achieved with moderate intensity chemotherapy in conjunction with IFN-α 2b, and sequential monitoring of MRD may be useful for disease surveillance. If confirmed, MRD studies would facilitate comparisons between treatments and allow for an earlier detection of disease.

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