NON-HODGKIN'S LYMPHOMA

Treatment of indolent lymphomas from watch and wait to high dose therapy

GERASSIMOS A. PANGALIS, THEODOROS P. VASSILAKOPOULOS, CHRISTINA KALPADAKIS, MARIA-CHRISTINA KYRTSONIS, STYLIANI I. KOKORIS, MARIA K. ANGELOPOULOU, & PANAYIOTIS PANAYIOTIDIS

First Department of Internal Medicine and Department of Haematology, National and Kapodistrian University of Athens School of Medicine, Laikon University Hospital, Athens, Greece

Indolent B-cell non-Hodgkin’s lymphomas (IBC-NHL) represent a heterogeneous group of chronic diseases [1]. Follicular lymphomas grades 1 and 2 (FL1/2) are by far the most common, accounting for approximately 20% of all NHL worldwide. Indolent IBC-NHL also include small lymphocytic lymphoma (SLL), which is the tissue counterpart of B-chronic lymphocytic leukemia (B-CLL); [2], lymphoplasmacytic lymphoma (LPL; 1%), mantle cell lymphoma (MCL; 6%), and marginal zone lymphomas, either splenic (SMZL; 1%), nodal (NMZL, 2%) or extra-nodal MALT (8%).

Various treatment strategies ranging from “watch and wait” policies or oral alkylating agent monotherapy to more aggressive combination chemotherapy (CT), chemoimmunotherapy or even CT followed by high dose therapy and autologous stem cell transplantation (ASCT) have been used in previously untreated patients with IBC-NHL. However there is no clear evidence for the superiority of any particular approach in terms of overall survival (OS), because: (i) The natural history of IBC-NHL is generally prolonged and many of these approaches are ultimately integrated in the overall treatment strategy, thus minimizing OS differences, despite significant differences in progression free survival (PFS); (ii) With the exception of FL, the rarity of these disorders raises further difficulties in the design of randomized trials.

We will review here current treatment approaches for FL1/2, MCL, SLL, LPL including Waldenstrom’s macroglobulinemia and NMZL, SMZL and extra-nodal MZ lymphomas of MALT type (EMZL), focusing mainly on first-line therapies.

Follicular lymphomas, grades 1 and 2

Ann Arbor stages I and II

This is the only subgroup of FL1/2, which is considered curable, accounting for approximately 1/4 of the total patient population. Involved field radiotherapy (IF-RT) may cure approximately half of stage I and one quarter of stage II patients. However based on recent developments some questions may be raised. Thus, it is not known whether IF-RT could be curative in patients with conventional stage I or II but with subclinical lesions in PET imaging. Furthermore, many of these patients have molecular evidence of disease dissemination as detected by the presence of BCL-2 or immunoglobulin heavy chain gene rearrangements in the blood or bone marrow DNA. It is not known whether such patients may be cured by and which is the place of rituximab in the potential eradication of residual disease.

Ann Arbor stages III and IV

Given that advanced FL1/2 are clearly incurable with conventional CT, a “watch and wait” policy is applied in patients with asymptomatic, non-bulky disease. This approach is supported by randomized trials [3]. Chemotherapy based treatment should be instituted when the patient develops constitutional symp-
toms or symptoms related to tumor burden. There is a plethora of treatment options (Table I), which differ with respect to response rates, PFS, and toxicity, but OS differences are not demonstrable so far.

Elderly patients can be safely treated with oral alkylating agents, such as intermittent chlorambucil, alkylator-based combination chemotherapy (CVP) or monotherapy with the anti-CD20 monoclonal antibody rituximab. Younger patients can also be treated with such approaches, but many centers prefer to administer anthracycline-based CT (CHOP or similar regimens, MCP: mitoxantrone, chlorambucil and prednisone, etc) or CT based on both anthracyclines and purine analogues (FND, FCM etc).

Several randomized trials have now convincingly demonstrated that the addition of rituximab to conventional CT produces superior PFS rates, but follow-up is still short to reveal potential differences in OS [4–7]. The efficacy of rituximab in the setting of relapsed/refractory FL [48% response rate (RR) with 13 mo median PFS] may in part obviate OS benefits of chemoimmunotherapy over CT alone. For the time being, it seems reasonable to add rituximab to the first-line CT regimen, irrespectively of the intensity of the latter.

A recent meta-analysis suggested that interferon-alpha (IFN-α) incorporated in the initial CT regimen and/or given as maintenance to responding patients may result in superior PFS rates and a modest increase in 10-year OS, in the order of 6–8% [8]. OS benefits were apparent only in the subgroups of patients receiving more intensive CT or higher doses of IFN-α. However the individual randomized trials included in this analysis were performed prior to the introduction of rituximab. Thus the benefit of IFN-α in the era of rituximab remains uncertain.

The value of autologous stem cell transplantation (ASCT) incorporate in the first-line approach of FL has been tested in 3 randomized trials [9–11]. Two of them demonstrated significant prolongation of PFS, while the third [11] revealed an OS benefit despite similar PFS! Firm conclusions on OS cannot be derived yet, but notably two trials demonstrated a significant increase of MDS/ANLL in ASCT-treated patients. Furthermore, rituximab, which prolongs PFS compared with conventional CT alone, was not used in anyone of these trials. Thus, ASCT is still experimental in the first-line treatment of FL. In contrast, ASCT is clearly indicated in relapsed/refractory disease.

Rituximab, when given as first-line monotherapy, produces RR of approximately 70% [12]. Maintenance with 4 bimonthly infusions prolongs the PFS over rituximab induction alone (median 36 vs. 19 months) [12]. It is however uncertain whether rituximab maintenance is superior to induction followed by retreatment upon progression. Given the favorable toxicity profile of rituximab and the potential of durable responses, it can be considered as frontline therapy at least in patients not eligible for aggressive CT.

Recently, radioimmunotherapy with 131I-Tositumomab (Bexxar) was shown to be very effective, not only for relapsed/refractory disease, but as first-line therapy as well. A single one week course of therapy produced a RR of 95% with 75% CRs in 76 previously untreated stage III/IV FL patients. Among CRs, 80% were extended at the molecular level as well, while the 5-year PFS was 59% and 5-year OS 89% [13]. In the setting of relapsed/refractory disease radioimmunotherapy with Bexxar or Y90 Ibritumomab tiuxetan (Zevalin), which can be administered in an outpatient basis, produces RR of 70–80% with approximately 30% CR. Radioimmunotherapy even at myeloablative doses with stem cell support has also produced very promising results in relapsed/refractory disease.

Table I. Treatment Options for Follicular Lymphomas-Grades 1 and 2

| Watch and Wait |
| Oral alkylating agents (intermittent chlorambucil, etc) |
| Alkylator – based combination chemotherapy (CVP)*§ |
| Anthracyclin – based combination chemotherapy (CHOP and similar regimens, MCP)*§ |
| Fludarabine – based combination chemotherapy (FND, FCM, etc)§ |
| Rituximab monotherapy |
| Chemotherapy followed by high dose therapy and autologous stem cell transplantation§ |
| Radioimmunotherapy |

*Interferon possibly added during and/or after chemotherapy, §Rituximab may be added in combination chemotherapy regimens, CVP: cyclophosphamide, vincristine, prednisone, CHOP: cyclophosphamide, vincristine, doxorubicin, prednisone, MCP: mitoxantrone, chlorambucil, prednisone, FND: Fludarabine, mitoxantrone, desamethasone, FCM: Fludarabine, cyclophosphamide, mitoxantrone.

Mantle cell lymphoma

MCL resembles to the IBC-NHL in that there is a continuous pattern of relapse and no plateau in survival curves. However MCL can not be strictly considered as an IBC-NHL, because median survival is short usually in the range of 2 to 4 years with <10% surviving at ten years after diagnosis. In contrast to FL, a “watch and wait” policy is not advisable in MCL except perhaps a minority of elderly patients with poor performance status. However approaches with very diverse toxicity profiles have been applied. The preferred treatment approach is highly depended on patient’s age.

CHOP or similar regimens are preferred by most centers, while others also use fludarabine-based regimens. The addition of rituximab to CHOP moderately prolonged PFS but had no effect on OS in a recent randomized trial [14]. The MD Anderson group has reported impressive preliminary results.
with the combination of rituximab and hyperCVAD regimen [15]. In the absence of randomized trials, this approach is considered experimental given that there is no plateau in PFS curves, the high toxicity of the regimen. Studies evaluating the first-line use of ASCT are ongoing, but no definitive OS data have been published so far. Allogeneic SCT – either myeloablative or based on reduced intensity conditioning regimens are the only potentially curable approaches and deserve further evaluation.

In contrast to these high-intensity approaches, some patients with MCL may achieve relatively durable remissions with chlorambucil monotherapy [16]. Thus, elderly asymptomatic patients without features of histologic aggressiveness (non-blastoid MCL) may be treated in this way. Rituximab monotherapy may produce RR of 25–30% in both untreated and relapsed/refractory MCL patients, but CRs are very rare (~2%) and the median PFS is in the range of 6–12 months. Maintenance rituximab does not appear to improve these results [17]. In the rare “splenic form” of MCL, splenectomy may be a reasonable first-line approach, delaying the administration of CT [18]. Novel agents, as the proteasome inhibitor bortezomib and temsirolimus a rapamycin kinase inhibitor that regulates cyclin-D1 translation are effective in relapsed/refractory patients and require further evaluation [19,20].

**Splenic marginal zone lymphoma**

SMZL is another entity for which the “watch and wait” policy was the preferred approach for patients having asymptomatic splenomegaly or non significant cytopenias. When treatment is needed, splenectomy is still a reasonable option. Various CT regimens, including CHOP or fludarabine-based ones as well as oral alkylating agents have been used, mainly in splenectomy failures or in patients not eligible for splenectomy [21]. The selection of the CT regimen is at present arbitrary. The goal of treatment is to achieve a good response, but not necessarily a CR. Interesting preliminary results have been reported with rituximab monotherapy, which may delay splenectomy [22]. The subgroup of patients with SMZL and hepatitis C virus infection achieve long-lasting partial remissions of excellent quality with interferon-a and/or ribavirine without CT [23].

**SLL, LPL/MW, NMZL**

Specific data for these subtypes of IBC-NHL, particularly for NMZL, are lacking. We favor treatment of these patients, who present usually with advanced age, with monthly intermittent chlorambucil for 1–2 years. High-dose chlorambucil produced a RR of 72% with 30% CRs in a recent randomized trial, with 5-year PFS rates of 20–30%. The addition of epirubicine or the administration of IFN-a maintenance did not improve these results [24]. Rituximab produces responses similar to that observed in FL and can be considered as monotherapy in these patients [25]. As many as 70% of previously untreated patients respond to induction plus maintenance rituximab, with a median PFS of approximately 2.5 years.

Combination CT (CVP, CHOP) is usually deserved for relapsed disease while purine analogues may also have a role in the treatment of these patients, although clear data are not yet available.

**EMZL**

MALT lymphomas commonly arise in the stomach but also can be seen in other extranodal sites such as the skin, salivary glands, lung, ocular adnexa and thyroid. Gastric lymphomas respond well to antibiotic therapy in conjunction with proton pump inhibitor therapy. A considerable percentage of patients achieve CR [26]. Radiation therapy or alkylating agent therapy alone or in combination with Rituximab is reserved for non-responders. For non-gastric MALT lymphomas the optimal management is not well defined. Single alkylating agent or CVP regimen, radiotherapy, immunotherapy, surgery alone or in combination have been successfully used [27]. Anthracycline based regimens do not seem to improve the response rate [28].

**Conclusion**

IBC-NHL may be treated with various strategies, without clear superiority of anyone of them. Evidence-based approaches are likely to emerge for FL (and probably MCL), but are difficult to be obtained for SLL, LPL and marginal zone lymphomas. The introduction of rituximab has revolutionized the treatment of IBC-NHL. ASCT and newer approaches including bortezomib and temsirolimus may improve their eventual outcome. For the time being, only ASCT can cure a fraction of relapsed/refractory patients at the expense of a high rate of early mortality.

**Acknowledgements**

This study was supported in part by a grant provided by IASIS, a non profit organization raising funds for research in leukemias, lymphomas and related disorders.

**References**


