Mantle cell lymphoma: an update on management

A. D. Zelenetz
Division of Hematologic Oncology, Memorial-Sloan Kettering Cancer Center, New York, NY, USA

Although response rates are increased, the addition of rituximab to induction chemotherapy has not yet been proven to extend the progression-free and overall survival benefits of chemotherapy alone. In first remission, high-dose therapy plus stem cell rescue improves time to treatment failure and progression-free survival when compared with maintenance interferon alpha. However, relapse rate does not reach a plateau. Radioimmunotherapy has substantial single-agent activity and when combined with chemotherapy may provide a platform onto which rituximab or autologous stem cell transplantation can be added. Targeted therapies are also showing promise and may have a role in maintenance and/or initial therapy.

Key words: mantle cell lymphoma, rituximab, autologous stem cell transplantation, radioimmunotherapy, targeted therapies, bortezomib, temsirolimus, flavopiridol

introduction

Mantle cell lymphoma (MCL) is reliably diagnosed by overexpression of the cell cycle regulatory protein cyclin D1, which results from the t(11;14) (q13;q32) chromosomal translocation placing the cyclin D1 gene under the transcriptional control of the heavy chain immunoglobulin gene [1]. MCL has been proven to be a stubbornly intractable disease. Treatment with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) produces a median survival of only 3 years and no currently available option is curative in advanced disease [2].

In this context, there is great interest in current investigational approaches. These include chemotherapy plus monoclonal antibody therapy; high-dose therapy supported by autologous stem cell transplant; allogeneic bone marrow transplantation; the use of thalidomide plus rituximab; as well as monotherapy with targeting agents like the protease inhibitor bortezomib, the cyclin-dependent kinase modulator flavopiridol, the mTOR signal transduction inhibitor temsirolimus (CCI 779) and radioimmunotherapy [3–5]. The potential of idiotype vaccines directed against an antigen derived from the patients’ own tumor has also begun to be explored in B-cell lymphoma including mantle cell lymphoma [6].

CHOP plus rituximab induction chemotherapy

In 2002, Howard et al. [7] reported that adding rituximab to CHOP (R-CHOP) induced a molecular complete response (CR) in 36% of the subgroup of 25 patients who had PCR-detectable BCL-1/IgH or clonal IgH products at diagnosis. Forty-eight per cent of the 40 patients in the full study had a clinical CR or an unconfirmed CR (CRu), and a further 48% had a partial response (PR), for an overall objective response rate (ORR) of 96%. However, this high ORR did not translate into extended progression-free survival (PFS), which was a median of 16.6 months. Furthermore, patients achieving a molecular remission following R-CHOP had no better outcome than those not in molecular remission (PFS 16.5 versus 18.8 months, \( P = 0.51 \)).

More recently, a randomized trial was conducted in which patients were assigned to six to eight cycles of either R-CHOP or CHOP alone [8]. Patients receiving R-CHOP who achieved CR or PR underwent a second randomization to peripheral blood stem cell transplantation or standard maintenance with interferon alpha (IFN-\( \alpha \)). Patients in CR or PR after treatment with CHOP alone were randomized to IFN-\( \alpha \) maintenance using either a standard or intensive regimen. R-CHOP produced a significantly higher rate of CR than CHOP alone (34% versus 7%, \( P = 0.00024 \)). The ORR was also somewhat higher (\( P = 0.015 \)) and time to treatment failure (TTF) was prolonged (median 21 versus 14 months, \( P = 0.013 \)). However, PFS was not significantly different in the two arms of the study (\( P = 0.31 \)). At 2 years, only one in four patients were free of progression, irrespective of assigned treatment. The curves showing overall survival (OS) are virtually superimposed up to 2 years, with around 75% of patients alive in both arms of the study.

hyper-CVAD plus rituximab induction chemotherapy

Romaguera et al. [9] from MD Anderson Cancer Center in Houston have recently reported a study in which 375 mg/m\(^2\) rituximab was added on day 1 to a treatment program
consisting of Hyper-CVAD (cyclophosphamide 300 mg/m² b.i.d. days 2–4, vincristine 1.4 mg/m² days 5 and 12, doxorubicin 16.6 mg/m²/day continuous infusion days 5–7, and dexamethasone 40 mg days 2–5 and 12–15) alternating with a regimen consisting of rituximab (375 mg/m² i.v. day 1), methotrexate (300 mg/m² by 2-h infusion followed by 800 mg/m² 22-h continuous infusion day 2) and cytarabine (3000 mg/m² 2-h infusion q 18 h days 3+4). The range of prophyaxis undertaken included the uroprotective agent mesna, leucovorin and antifungal antibacterial as well as antiviral agents. Patients were staged after every two cycles. If in CR, a total of six treatment cycles were administered. Transplantation was offered to patients not in CR at the end of six cycles. Cytarabine dose was reduced for older patients and in those with renal dysfunction.

At median follow-up of 40 months, the 3-year failure-free survival (FFS) rate was 64%, and 82% of patients were alive. These results are encouraging in comparison to historical controls.

Similarly good outcomes have been achieved by adding rituximab to a modified (Wisconsin) Hyper-CVAD schedule [10]. In this schedule, the chemotherapy element consists of cyclophosphamide 300 mg/m² twice daily for 3 days, doxorubicin 25 mg/m² days 1–2 and vincristine 2 mg flat day 3, plus dexamethasone 40 mg days 1–4. Rituximab 375 mg/m² is added from cycle two onwards, with the dose split if the peripheral blood leukocyte count is >25 000. Patients are restaged every two cycles. Those entering CR receive an additional two cycles, with a maximum of six given. Patients in CR, CRu or PR receive maintenance rituximab at a dose of 375 mg/m² for 4 weeks every 6 months for 2 years.

Among 20 evaluable patients, the best response was CR or CRu in 14 (70%), with a further three patients entering PR, giving an ORR of 85%. By intent-to-treat, 17 of 22 patients had a CR or PR, giving an ORR of 77%. After follow-up ranging from 4 to 45 months (median 22.5 months), the calculated 2-year survival rate for the intent-to-treat population is 82% and the PFS rate is 73%.

Only randomized, prospective studies, however, can show whether survival is truly extended by the addition of rituximab to Hyper-CVAD schedules. Furthermore, it should be noted that the hematological toxicities associated with this development in therapy, although expected, are clinically significant. In the MD Anderson study, four patients developed treatment-related myelodysplasia/AML [9]. Moreover, the continuing occurrence of relapses suggests that minimal residual disease persists and will need to be managed with additional therapy [9, 10].

consolidation

Strategies for consolidation have been addressed in the European Mantle Cell Lymphoma Network’s phase III study in which patients in PR or CR following six courses of CHOP-like chemotherapy were randomized to approaches involving either IFN maintenance or autologous stem cell transplant (ASCT) [11]. In more detail, one arm consisted of two cycles of consolidation followed by IFN. The other arm consisted of DexaBEAM and peripheral blood stem cell harvest, followed by cyclophosphamide 120 mg/kg plus total body irradiation and ASCT.

Data on 122 patients’ best response following consolidation in first remission show that ASCT results in a PR rate of 17% and a CR rate of 81%, while IFN results in a PR rate of 62% and a CR rate of only 37%. Survival curves for time to treatment failure following randomization show ASCT to be superior to IFN (P = 0.0023). Data on TTF following end of induction therapy also show a trend in this direction (P = 0.18). The fact that patients who relapsed on IFN could cross over to the transplant arm will complicate analysis for overall survival. Importantly, neither the TTF nor PFS curves show a plateau.

radioimmunotherapy

Mantle cell lymphoma is highly radiosensitive. Use of external beam radiotherapy, however, is limited by the systemic nature of the disease. Radioimmunotherapy (RIT) addresses this problem since it systemically targets radionuclides to the tumor. The potential role of RIT has been investigated both as a component of initial therapy and of salvage therapy in relapsed disease.

In a phase II study performed at the MD Anderson Cancer Center in heavily pretreated relapsed or refractory MCL, 15 patients who had not previously had high-dose therapy or ASCT received single agent 90Y-tositumomab tiuxetan [12]. The dose was 0.3 mCi/kg in patients with a platelet count of 100–149 000/mm³ and 0.4 mCi/kg if the count was 150 000/mm³ or above. Responses were seen at both doses, particularly in patients without bulky disease. The ORR was 33%, with three out of 15 patients having a CR and two a CRu.

Work at the Memorial-Sloan Kettering Cancer Center has investigated the potential of tositumomab/Iodine131 tositumomab as part of the initial therapy. Twenty-four patients received RIT followed by restaging at 7 and 13 days and then six cycles of CHOP [13]. Sequential RIT and chemotherapy was safe and showed substantial single-agent activity. High response rates and instances of molecular remission were seen. In this context (and in contrast to that seen when adding rituximab to CHOP), molecular remission appears to improve clinical outcome. Tositumomab plus chemotherapy could therefore represent a promising platform onto which rituximab or ASCT could be added.

targeted therapies

In two phase II studies of single-agent bortezomib in indolent lymphoma, the proteasome inhibitor was administered at a dose of 1.5 mg/m² twice a week for 2 weeks every 3 weeks (this 3-week period constituting one cycle) [14, 15].

Among the 39 patients with multiple relapsed or refractory MCL who were included in the trials, the ORR was 44% (seven patients had a CR/CRu and 10 a PR). MCL patients had a median time to response of 5 weeks, compared with 11 weeks for patients with follicular lymphoma. Given this encouraging start, strategies to integrate bortezomib earlier into the treatment and into maintenance therapy are being developed.
Thirty-five patients with relapsed or refractory mantle cell lymphoma were enrolled in a phase II trial to receive the inhibitor of the mammalian target of rapamycin kinase temsirolimus. The dose was 250 mg intravenously every week for a total of 12 cycles or two cycles after CR in responding patients. Temsirolimus had substantial antitumor activity. The overall response rate was 38% with one CR and 12 PR, the median time-to-progression was 6.5 months and the duration of response was 6.9 months [16].

In preclinical models flavopiridol exhibited CDK inhibitory activity, depleted cyclin D1 and vascular endothelial growth factor RNA, respectively, inhibited elongation factor B, thus leading to transcription halt and induced apoptosis [17]. Several schedules have been tested and a daily bolus of 50 mg/m² for 3 consecutive days every 3 weeks resulted in a modest activity in previously untreated and relapsed mantle cell lymphoma [18]. Phase II/III trials using a 1-h schedule are being conducted in several tumors including mantle cell lymphoma.

**Conclusion**

In MCL today, several chemotherapy regimens are able to induce high rates of remission. The addition of rituximab increases rates of CR and PR. However chemotherapy plus rituximab does not cure patients any more than chemotherapy does alone.

In consolidation, high-dose therapy with ASCT appears to improve TTF, but any impact on survival remains to be proven. A variety of new approaches, notably RIT agents and bortezomib, have activity and may have a role both in initial therapy and in enhancing consolidation in this difficult disease.

**References**