Front-line treatment of mantle cell lymphoma

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In this issue of the Journal, Gressin *et al.*[1] publish the results of two phase II trials on newly diagnosed mantle cell lymphoma (MCL). In the first trial (LM1996), the treatment was infusion based vincristine and doxorubicin, oral dexamethasone and chlorambucil (VADC). Elderly patients received eight series while younger patients received six followed by high-dose melphalan and total-body irradiation with autologous stem cell transplantation (ASCT). In the subsequent LM2001 trial, younger patients (<65 years) received six cycles of VADC + rituximab (R-VADC) followed by ASCT. The reported outcome following VADC and R-VADC of all patients is about 45% complete response rate and an over 70% overall response rate. There was a significant progression free and overall survival advantage of ASCT (transplant was only offered to younger patients). Among transplanted patients, there is a trend for a progression free survival advantage of rituximab but no overall survival advantage. The results translate into median survival rates of less than three years for those who do not undergo transplant and seven years for those who do, both groups showing a continuing pattern of relapse and death with relapse occurring up to ten years after completion of therapy.

Induction therapy

Even though the role of anthracyclins in mantle cell lymphoma has been under doubt ever since this entity was first recognized as centrocytic lymphoma,[2] CHOP has been regarded by many to be the standard therapy. Based on prospective data, Hermann *et al.*[3] found the median survival time to have increased from around three years in the 1980s to almost five years in 2000. This is due to a shift in induction therapy from mainly chlorambucil or COP to CHOP or R-CHOP. The VADC is a CHOP-like regimen with chlorambucil replacing cyclophosphamide as alkylator. Prolonged infusion of doxorubicin and vincristin, already advocated by Wilson *et al.*[4] in order to overcome increased expression of the multidrug resistance gene and to reduce cardiotoxicity, is used in both the VADC and the hyperCVAD regimens.[5] However, it has not been documented to be more effective than standard bolus administration. The addition of rituximab to CHOP increased the complete response rate but not progression free or overall survival.[6]

It, therefore, seems that R-CHOP-like regimens, infusion or bolus based, can lead to complete response rates of approximately 40% and overall response rates of approximately 90% (within the confidence limits of the response rates reported here by Gressin *et al.*) and, in spite of further consolidation with ASCT, all patients will eventually relapse. Should CHOP-like chemotherapy, with or without rituximab or ASCT, still be considered the standard of care in mantle cell lymphoma?

Other cytostatic drugs challenging the CHOP components studied in prospective trials include cytarabine (AraC) and methotrexate (Mtx). In particular, cytarabine appears to be uniquely active in mantle cell lymphoma. Two front-line studies which included cytarabine rather late in their schedule to partial and non-responders after three or four cycles of CHOP illustrate this. After four cycles of CHOP, Lefrere *et al.*[7] achieved only 7% complete remission (CR) and 50% partial remission (PR). The partial and non-responders went on to receive two or three cycles of DHAP (dexamethasone, AraC, cisplatin, with AraC 4g/m^2 per cycle) which eventually led to 81% complete and 2 partial responses (8%) before ASCT. Van't Veer *et al.*,[8] achieving only 15% complete remission after three cycles of R-CHOP, gave a single subsequent cycle of high-dose cytarabine (total 16 g/m^2) which almost doubled the complete remission rate to 29% before the subsequent high-dose therapy + ASCT. In spite of the increase in responses, continuous patterns of relapse were seen, suggesting that cytarabine, albeit highly active in mantle cell lymphoma, should be used early.

Two regimems which introduce early high-dose cytarabine are HyperCVAD + Mtx/AraC and the Nordic maxi-CHOP/AraC. Both regimens consist of six to eight 21-day cycles of the CHOP components alternating with cycles containing high-dose cytarabine 12g/m^2 per cycle given as four 2-3 hour infusions. The regimens differ mainly in the use of methotrexate.

In their single-institution report on R-hyperCVAD + Mtx/AraC without subsequent ASCT, Romaguera *et al.*[5] reported 87% complete remission (CR)/unconfirmed complete remission (Cru) and an overall response rate 97% after the first six cycles. However, in a multicenter setting, Epner *et al.*[9] found only 58% CR/CRu and 30% PR. In both studies, quite high toxicity was reported and treatment had to be stopped in as many as 29% of the patients, in particular those in the MTX/AraC arm. In the somewhat younger patients of the Nordic study,[10] which did not include methotrexate, only 3% stopped treatment prematurely due to toxicity. Interestingly, in a recent CALGB report[11] of induction with two or three cycles of MTX + CHOP, severe renal toxicity early in the study led the investigators to reduce the methotrexate dose 90%, from 3,000 to 300 mg/m^2. The final complete remission rates following the higher and lower methotrexate doses were 67% and 78%, respectively. This indicates that in mantle cell lymphoma, high-dose methotrexate may result in greater toxicity than efficacy, and that Ara C is the drug that has the biggest impact on CR rates.

Fortunately, the role of cytarabine as part of the induction therapy for mantle cell lymphoma may be soon be clarified by the awaited results of a large European MCL Network phase III trial comparing R-CHOP with R-CHOP

alternating with R-DHAP. Until then, to this author, the available phase II results clearly indicate that early high-dose Ara C should be part of the standard induction therapy for younger MCL patients.

Autologous stem cell transplantation

The landmark trial of Dreyling *et al.*[12] is still the only randomized trial of consolidation with high-dose therapy. Patients who responded to CHOP were randomized between more CHOP + maintenance with interferon-α or to stem cell mobilization with dexa-BEAM, followed by myeloablative radio-chemotherapy and ASCT. Progression free survival was clearly and highly significantly prolonged in the ASCT arm but as yet no survival advantage has been observed, probably due to the cross-over design of the study. The huge survival advantage of ASCT in the GOELAMS study, although uncontrolled and to a degree age-selected, fits these results. Disappointingly, none of the studies of CHOP-like regimens followed by ASCT[1,12,13] showed continuing patterns of relapse, with no signs of a plateau in the progression free and overall survival curves.

In the Nordic MCL-1 study based on CHOP + BEAM and ASCT,[13] the 5-year progression free survival was only 20%. In the subsequent MCL-2 study,[10] which only differed in the addition of high-dose Ara C and rituximab, the 5-year progression free survival was 66% without any progression after five years. With identical high-dose therapy in MCL-1 and MCL-2 (BEAM or BEAC), the reason for the difference must lie in the use of Ara C and rituximab.

Taken together, the data indicate that ASCT is not a panacea to remedy a mediocre response to induction. Rather, its role should be to consolidate the best possible clinical and molecular remission achievable by intensive immunochemotherapy and to eradicate reminiscent undetectable deposits of MCL stem cells. Whether such increasingly intensive induction therapy may make ASCT unnecessary can in reality only be proved by a new trial based on such optimal induction immunochemotherapy.

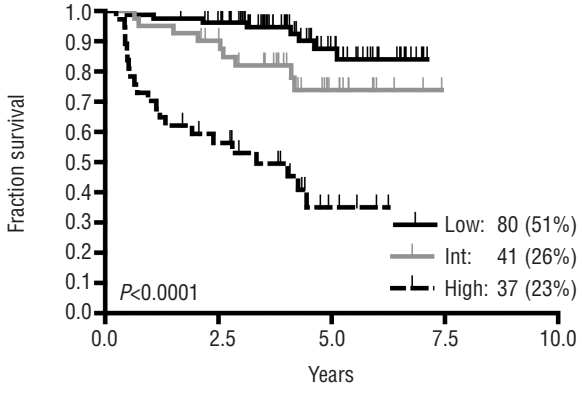

Figure 1. Survival of the Nordic MCL-2 patients according to the Mantle Cell Lymphoma International Prognostic Index (MIPI).[19] Reproduced with permission of the American Society of Hematology.

Present data do not support abandoning ASCT. In the Nordic MCL-2 trial,[10] the sixth (stem-cell mobilizing) R-AraC cycle plus the BEAM + ASCT increased the complete remission rate from 56% to 90%; in the European MCL Net series[14] ASCT led to a significant reduction in minimal residual disease compared to the induction immunochemotherapy (including, in some cases, Ara C). Hence, ASCT should be considered the standard of care in younger patients until a controlled trial shows otherwise. Given the high efficacy of *in vivo* purging,[10] withholding ASCT because of concern about reinfusion of tumor cells is no longer justified.

The value of rituximab was clearly demonstrated by Lenz *et al.*[6] as the addition of rituximab to CHOP increased the complete remission rate from 7% to 35% but did not improve outcome. Just like ASCT, antibody therapy can apparently not compensate for ineffective chemotherapy, whereas, added to the right treatment, it can increase response to a level of molecular remission including *in vivo* purging of stem cells.[10,14-16] The reported late relapses by Gressin *et al.*[1] suggest the presence of dormant lymphoma stem cells which might be targeted by maintenance therapy with CD20 antibodies. Newer type I and type II antibodies may increase the impact of CD20 targeted antibody therapy in mantle cell lymphoma.[17]

In the ongoing process of improving therapy for mantle cell lymphoma, the prognostic indices like the Mantle cell International Prognostic Index (MIPI)[18] and the GOELAMS Index introduced here by Gressin *et al.* emerge as important tools that clearly identify patients in whom present induction therapies (not only CHOP-like, but indeed also the Nordic maxi-CHOP/AraC based) fall short (Figure 1).[19] Both indices identify lactate dehydrogenase (LDH) (although not graded by the GOELAMS Index), performance status, and expression of ki-67 (MIPI-biological) as independent prognostic factors; the GOELAMS Index also includes B symptoms. Surprisingly, age was not an independent prognostic factor in the GOELAMS Index, even though ASCT, significant in the preceding univariate analysis, was only offered to younger patients.

Irrespective of the differences between them, such prognostic indices now enable us to identify poor-risk patients from the time of diagnosis and to introduce risk adapted therapy. For example, in MIPI high-risk patients, who have a much shorter survival than MIPI low- and intermediate-risk patients[19] (Figure 1), further intensification of induction therapy, e.g. increasing the cytarabine and reducing the CHOP components, could be explored.

Elderly mantle cell lymphoma patients

Which drugs can potentially improve the outcome in elderly patients who do not tolerate an intensive treatment approach? Following the encouraging results of R-FCM as salvage therapy,[20] the European MCL Network is presently comparing R-CHOP with R-FC in a large phase III trial of front-line therapy in the elderly, followed by a second randomization to maintenance with either rituximab or interferon-α. Rummel *et al.*,[21] comparing R-CHOP with R-bendamustine, found higher complete remission rates and response duration with R-bendamustine. Kahl *et al.*[22] reported very high response rates by the addition of bortezomib to R-hyper-CVAD in a representative mantle

cell lymphoma population including elderly patients: 75% complete remission and 96% overall response rates without serious neurotoxicity. Lenalidomide[23] and temsirolimus[24] appear promising in relapsed mantle cell lymphoma including in elderly patients, and further testing in combinations and as front-line therapy is warranted.

Conclusions

In conclusion, for the younger patients with mantle cell lymphoma, we have seen a glimpse of a cure with intensive therapy. A roadmap leading to the cure of mantle cell lymphoma is emerging. This needs to be explored with the help of prognostic indices and intensive, risk-adapted therapies in order to induce complete clinical, metabolic (PET) and molecular remission followed by ASCT with tumor free stem cell support. This could then probably be followed by a continuing effort to eradicate reminiscent MCL stem cells by maintenance therapy with antibodies or immunomodulating drugs, or even re-induction like in acute lymphoblastic leukemia. Targeted therapy, developed in elderly and relapsed patients, will clearly benefit all subgroups, including the front-line setting.

Dr. Geisler is head of the MCL program at Department of Haematolgy at Rigshospitalet, Copenhagen, Denmark, and of the Nordic Lymphoma Group MCL subcommittee.

No potential conflict of interest relevant to this article was reported.

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