Mantle cell lymphoma

HIGH-DOSE CYTARABINE (ARA-C) IMPROVES OS

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Mantle cell lymphoma (MCL) outcome has improved during the last decades. In its first randomized trial, the MCL net demonstrated that myeloablative consolidation followed by autologous stem cell transplantation (ASCT) resulted in a significant prolongation of progression-free survival (PFS) in advanced-stage MCL (Dreyling et al. Blood 2005). Recent Phase II studies suggest that the addition of rituximab and/or high-dose ara-C may significantly improve outcome. A Phase II trial using sequential R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone)/R-DHAP (rituximab, dexamethasone, cytarabine and cisplatin) followed by ASCT showed an overall response rate (ORR) of 95% with a complete response (CR) rate of 61%, a median event-free survival (EFS) of 83 months and a 75% survival rate at 5 years (Delarue et al. Blood 2012). Two years ago the preliminary results of the the MCL randomized trial compared 6 courses of CHOP plus rituximab followed by myeloablative radiochemotherapy (12 Gray total-body irradiation [TBI], 2x60 mg/kg cyclophosphamide) and ASCT (control arm A) vs alternating courses of 3x CHOP and 3x DHAP plus rituximab followed by a high-dose ara-C containing myeloablative regimen (10 Gray TBI, 4x1.5 g/m² ara-C, 140 mg/m² melphalan) and ASCT (experimental arm B). Those results showed that after a median followup of 27 months, patients in Arm B experienced a significantly better time-to-treatment failure (TTF) (49 months vs no response [NR]; $p=0.0384$, HR 0.68), but no overall survival difference. Final results are now available, with a median followup of 51 months.

Patients had previously untreated MCL Stage II–IV up to the age of 65 years. The primary endpoint was TTF. Stable disease after induction, progression or death from any causes were considered as treatment failures. Sample size was calculated to detect a relative risk of 52% for Arm B with a power of 95%. Randomization was stopped as soon as a significant difference was observed between the two arms.

The 485 patients evaluable for the primary analysis displayed the following characteristics (A vs B): median age 56 vs 56 years, male 79% vs 79%, Stage IV 82% vs 81%, symptomatic 43% vs 31%, ECOG (Eastern Cooperative Oncology Group) status >2 4% vs 4%, high LDH (lactate dehydrogenase) 39% vs 35%, and MIPI (MCL International Prognostic Index) low/intermediate/high 60%/25%/15% vs 64%/23%/13%, respectively. After induction, overall response (OR) was similar in both arms (90% vs 95%; $p=0.19$) but CR and unconfirmed CR (CRu) rates were significantly higher in Arm B (25% vs 36%; $p=0.012$ and 40% vs 54%; $p=0.0003$). The number of patients transplanted was similar in both arms (72% vs 73%). After transplantation OR and CR rates were comparable in both arms (98% vs 97% and 63% vs 61%). After a median followup of 51 months, TTF was longer in Arm B (46 vs 88 months; $p=0.0382$, HR 0.68) mainly due to a lower number of relapses after CR/CRu/partial response (n=81 vs 40). The rate of ASCT-related deaths in remission was similar in both arms (4% vs 4%). Although CR rate after ASCT was similar in both arms, remission duration (RD) after ASCT was superior in Arm B (49 vs 84 months; $p=0.0001$). At the time of final analysis, OS was superior in Arm B (NR vs 82 months; $p=0.045$). Safety after induction was comparable in both arms except for an increased grade 3/4 hematologic toxicity (hemoglobin 9% vs 30%, white blood cells 50% vs 75%, platelets 10% vs 74%), renal toxicity (creatinine Grade 1/2: 10% vs 44%, Grade 3/4: none vs 1%), and Grade 1/2 nausea and vomiting in Arm B. Toxicities of both conditioning regimens were similar.

Longer followup confirmed that high-dose ara-C in addition to R-CHOP significantly increases complete response rates, TTF and, in addition, overall survival without a clinically relevant increase in toxicity. Therefore, induction regimens containing high-dose ara-C followed by ASCT should become the new standard of care in MCL patients <65 years.

Reports from the American Society of Hematology Annual Meeting
The role of new agents in the initial management of MCL. This should change with the compelling results from the MCL Younger trial presented at the 2012 ASH meeting. In this study, standard R-CHOP (Arm A) or sequential cycles of R-CHOP and R-DHAP (Arm B) was followed by myeloablative chemotherapy and ASCT. Although response rates following ASCT were identical in the two treatment arms, how that response was achieved did matter. Relapse rates were twice as high in Arm A as in Arm B, resulting in a 3-year improvement in remission duration for those receiving DHAP. OS was also improved (median 82 months for Arm A, not yet reached in Arm B). These results were achieved with no difference in treatment-related mortality (4% in each arm). There was however a higher rate of Grade 3/4 hematologic toxicity in the high-dose cytarabine arm (Arm B).

R-CHOP plus R-DHAP followed by high-dose chemotherapy and ASCT should be considered the new standard of care for young, newly diagnosed MCL patients. Induction with more intensive regimens is probably unnecessary. The results of the current trial compare favourably to results seen with Hyper-CVAD + methotrexate/cytarabine, but with considerably less toxicity. Further advances in treatment may be seen with the use of new agents such as bortezomib and rituximab.

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**References**