Malignant Lymphomas

Rituximab and DHAP followed by intensive therapy with autologous stem-cell transplantation as first-line therapy for mantle cell lymphoma

We report on a series of 24 patients with newly diagnosed mantle cell lymphoma treated with four to six courses of DHAP-rituximab followed by autologous stem cell transplantation for patients <65 years. Three-year overall survival (OS) and event free survival (EFS) rates were 69% and 65% respectively, for the 24 patients. In intent-to-treat analysis, 3-year OS and EFS were 75% and 76% for the 17 patients < 65 years old. This treatment is quite feasible and compares favourably with other regimens.

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Mantle cell lymphoma (MCL) is characterized by its aggressiveness and refractoriness to standard chemotherapy.[1] Encouraging results have recently been obtained by using high-dose aracytine regimens followed by autologous stem cell transplantation as first-line therapy for MCL.[2-4] It has also been shown that the chimeric monoclonal antibody anti-CD20 (rituximab) improves response rates over those achieved by chemotherapy alone[5] and could represent an interesting *in vivo* purging method.[6] Here, we report on a series of 24 patients with newly diagnosed MCL, treated in two French centers according to a protocol using a combination of DHAP and rituximab (R-DHAP) as first-line therapy regardless of age and followed by autologous stem cell transplantation (ASCT) for patients under 65 years of age. All patients gave informed consent. The median age of the whole series was 61.8 years. Seventeen patients were <65 years old (group 1), and had a median age of 58.5 years; 7 patients were ≥65 years old (group 2, median age 69.3 years). The diagnosis of MCL was based on a combination of histological, immunophenotypic, cytogenetic and molecular criteria. Eighteen patients had a standard $CD5^+$ $CD23^-$ pattern. Four patients expressed CD5 and a low level of CD23 antigen while two other $CD5^+$ patients were not evaluated for CD23: the diagnosis of MCL was confirmed by cyclin D1 overexpression in these six cases. Molecular analysis, performed in all but two patients, showed overexpression of cyclin D1 by competitive reverse transcriptase polymerase chain reaction in 21 patients and rearrangement of the *BCL1* gene with *Ig*H by polymerase chain reaction in one patient. All patients presented with disseminated disease and the majority (96%) had bone marrow involvement.

Twenty-four patients (100%) completed the four initial courses of R-DHAP. Twenty-two (92%) of them entered complete remission (CR) or complete remission unconfirmed (CRu) and one patient was in partial remission (PR). The overall response rate (CR+PR) after four courses of R-DHAP was 96%. The R-DHAP regimen was associated with acceptable toxicity, even among the elderly patients. The main toxicities were reversible grade 3-4 cytopenia with red blood cell and platelet transfusions being required in 42% and 33% of cases, respectively. Other toxicities were renal failure (grade 1-2, n=3; grade 3, n=1) and glycemic imbalance (n=3). No toxic deaths occurred. Three year OS and EFS for the whole series were 69% and 65%, respectively (Figure 1A).

Table 1. Patients' characteristics.

Parameters	Number (%)
Median age (range)	61.8 yrs (47-74)
group 1: age <65 yrs	n=17 (71%)
group 2: age >65 yrs	n=7 (29%)
Sex	
M/F	17/7 (71%/29%)
Performance status	
0-1	24 (100%)
Ann Arbor stage	
III/IV	24 (100%)
Bulky tumor	10 (42%)
Extranodal disease	9 (38%)
B symptoms	9 (38%)
High lactate dehydrogenase	13 (54%)
Bone marrow involvement	22/23 (96%)
Leukemic phase	16 (67%)
Internal Prognostic Index	
low/low-intermediate	9 (37%)
intermediate-high/high	15 (63%)

In group 1, 16 (94%) out of the 17 patients entered CR or CRu. Fourteen patients underwent stem cell mobilization after three to four courses of R-DHAP. The stem cell harvest failed in three cases. Finally, ten patients underwent ASCT after a total of four to six courses of R-DHAP. The median time between completion of the last course of R-DHAP and high-dose therapy was 54 days (25-100). All patients were in CR before ASCT. The conditioning regimen was BEAM for patients over 60 years (n=4) and total body irradiation-containing regimens for patients under 60 years (n=6). Apart from the classical usual cytopenia, we observed few toxicities during the intensification procedure. One patient developed persistent renal insufficiency after stem cell transplantation and another developed *Pseudomonas aeruginosa* septicemia. No toxic deaths occurred. Three group 1 patients relapsed. One patient relapsed 6.5 months after autografting and received seven courses of standard CHOP as salvage therapy. He died from acute heart failure of unexplained origin while in PR. Two other patients not eligible for ASCT relapsed 3 and 6 months off therapy, respectively. Finally, nine out of the ten autografted patients are in persistent CR with a median follow-up after ASCT of 28 months (11.5 to 48 months). In intent-to-treat analysis, we report 3-year overall and event free survival rates of 75% and 76%, respectively (Figure 1B).

In group 2, six (86%) out of the seven patients entered CR or CRu after the four courses of R-DHAP and five of them received two additional courses of the same regimen. Two patients relapsed, 6 and 19 months off therapy, respectively. Three patients are still alive in CR 15 to 47 months after therapy. These results compare favorably with those of the study recently reported by Romaguera *et al.* in which elderly patients received adjusted hyperCVAD with rituximab.[7] The efficacy of velcade delivered either alone or in combination with chemotherapy or rituximab, is currently being evaluated.[8] We, therefore, must wait to know which strategy should be recommended for elderly patients.

We conclude that a R-DHAP regimen produces a highly efficient response rate, since 92% of patients entered

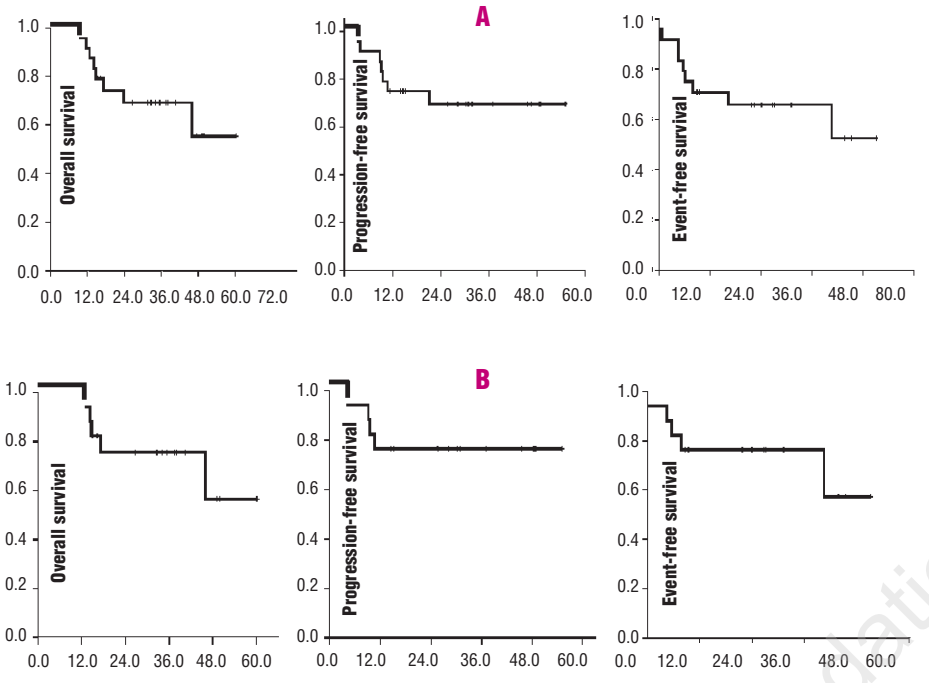

Figure 1. A. Overall, progression-free and event-free survival of the 24 patients. **B.** Overall, progression-free and event-free survival of the 17 patients ≤ 65 years old (intent to treat)

CR after four courses of this regimen. This result compares favorably with results of previously reported studies using R-CHOP or R-DHAP regimens[9] and the R-DHAP regimen seems as efficient but less toxic than the adjusted hyperCVAD plus rituximab regimen reported by Romaguera.[7] In conclusion, a combination of rituximab and DHAP followed by ASCT seems an attractive approach for young MCL patients. Moreover, R-DHAP can also be used for elderly patients with good results and low toxicity. More follow-up is needed to determine the respective roles of ASCT, rituximab or their combination in the management of high-risk MCL patients and to define the optimal schedule of rituximab as induction or maintenance therapy, or both.

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