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Malignant Lymphomas

Sequential chemotherapy regimens followed by high-dose therapy with stem cell transplantation in mantle cell lymphoma: an update of a prospective study

This study is a long-term follow-up analysis evaluating clinical outcome of patients with mantle-cell lymphoma treated by the sequential CHOP and DHAP chemotherapy followed by autografting. The median overall survival of 81 months (95% CI, 66-not reached) and the median event free survival of 51 months (95% CI, 43-not reached) confirm the improvement in outcome obtained by such protocol.

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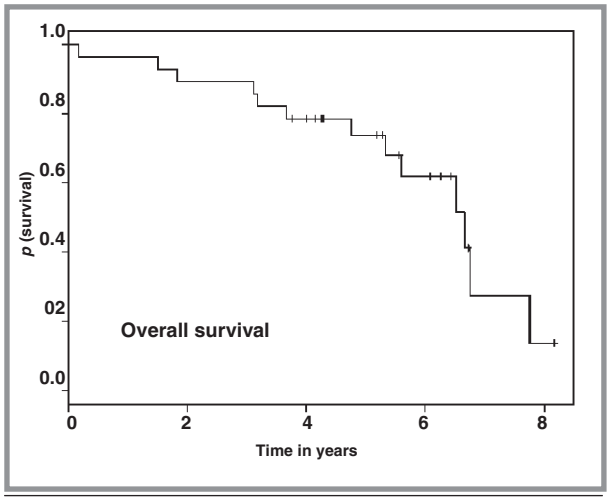

Figure 1. Overall survival (Kaplan-Meier).

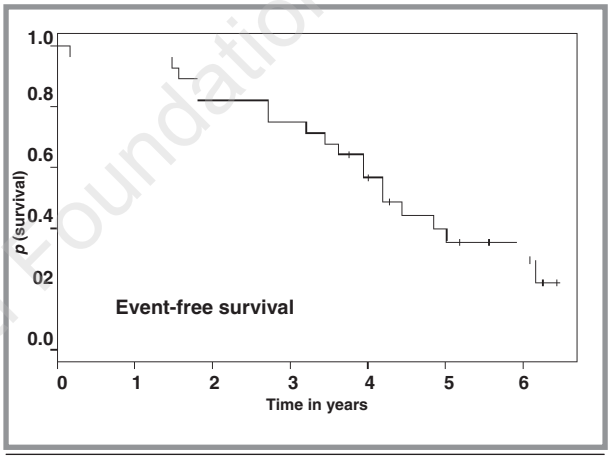

Figure 2. Event-free survival (Kaplan-Meier).

Despite an initial relatively indolent clinical presentation, the prognosis of mantle cell lymphoma (MCL) remains poor with a median survival of less than 3 years.[1-4] We previously reported a prospective study of 28 patients treated between 1995 and 1999 based on the response to initial CHOP therapy with the aims of increasing response rate before autologous peripheral blood stem cell transplantation (APBSCT) and increasing event free and overall survival.[5] Patients who achieved a complete remission (CR) after four cycles of CHOP received total body irradiation (TBI) plus high dose cyclophosphamide and etoposide as a myeloablative regimen before APBSCT. Patients who did not achieve a CR after CHOP were treated with salvage therapy consisting of a high dose cytarabine regimen (DHAP) followed by TBI plus high dose cytarabine plus melphalan (TAM8) and APBSCT. Only two CR and 14 partial responses (PR) were obtained after CHOP. The two patients in CR after CHOP underwent intensification with TBI, high-dose cyclophosphamide-etoposide and unpurged APBSCT. The other twenty-five patients received DHAP and in this group a response rate of 92% (21 CR (84%), two PR (8%)) was observed. Two patients had progressive disease. The twenty-three responding patients received high-dose therapy (TAM8 regimen) followed by APBSCT. There was no conditioning or transplant-related mortality. Here we report the outcome of these patients after a longer median follow-up.

Sixteen (58%) of 28 patients remain alive at the time of data analysis (January, 2004) The median overall survival from diagnosis is 81 months (95% confidence interval, 66-not reached) from the time of diagnosis (Figure 1). In addition, 9 (32%) patients remain alive and progression free (5 patients remaining alive and in remission 6 or more years after treatment). These data result in a median event-free survival of 51 months (95% confidence interval, 43-not reached) (Figure 2).

Our data are similar to those of a published study on the hyper-CVAD/mitoxantrone-cytarabine regimen that contains high dose cytarabine,[6] in which the authors reported a high response rate of 93.5% (CR 38%, PR, 55%) for patients with MCL previously treated (or not). However, the response rate for the subgroup of previously untreated patients was not given and some patients (including some previously treated with chemotherapy) failed to mobilize enough PBSC to harvest for autografting. It is noteworthy that in our study, two courses of DHAP after four cycles of CHOP did not compromise stem cell harvesting, since no patient failed to have adequate peripheral stem cell collection. In a second study, previously untreated 65 years or older patients with MCL were enrolled in sequential phase II trials using hyper-CVAD, alternating with high doses of

mitoxantrone-cytarabine ARA-C with adjustment of the dose of cytarabine. The overall response rate was 92% (95% C.I. 73-99) and the complete remission (CR) rate was 68%. With a median follow-up of 17 months, the median failure-free survival for the entire group was 15 months. Finally, a phase-II study of a 96-hour continuous infusion of cisplatin with two timed-sequential couplets of fludarabine and Ara-C together was performed in patients with previously refractory MCL. The overall response rate was 88%. The actuarial 2-year survival rate was 50±18%. These results are promising and suggest that the addition of fludarabine as a potential biochemical modulator may enhance the activity of cisplatin and cytarabine.[8,9] Moreover, preliminary results from a randomized study conducted by the European Mantle Cell Lymphoma Network may confirm that consolidation with myeloablative radiochemotherapy followed by APBSCT improves progression-free survival in patients younger than 65 years.[10]

In our study, the median overall and event-free survival of 80 and 51 months, respectively, strongly suggest that the present strategy of treatment improves the global prognosis of patients with MCL. These results are encouraging because long-term, disease-free survival is uncommon for patients with MCL especially for those with advanced disease. Remarkably, 9 patients remain alive and progression free with 5 patients remaining in remission 6 or more years after treatment. These patients were not selected for their good prognosis, none of them had mantle zone histological subtype and β2-microglobulin was elevated in all cases. However, a majority of patients still relapse necessitating the improvement of our strategy. We are currently conducting a prospective phase II multicenter study to evaluate the combination of chemotherapy with anti-CD20 before intensification by TAM8 plus APBSCT.

In conclusion, these stimulating results after a longer follow-up confirm the efficiency and the role of high dose cytarabine and cisplatinum in improving the outcome of MCL patients in first line therapy. However, despite a significant improvement in prognosis with such therapy, more progress is necessary to lengthen survival further in patient affected by MCL.

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