Time to progression of mantle cell lymphoma after high-dose cytarabine-based regimens defines patients risk for death

The current standard treatment of younger patients with mantle cell lymphoma (MCL) includes rituximab and high-dose cytarabine (HD-AraC), usually followed by autologous stem cell transplantation (ASCT). This approach has improved the long-term outcome of these patients. However, no plateau in survival curves has been observed, and virtually all patients will experience disease recurrence for which no standard therapy exists (Dreyling *et al*, 2017). Allogeneic stem cell transplantation (AlloSCT) remains the only option with curative potential (Robinson *et al*, 2015; Tessoulin *et al*, 2016; Rule *et al*, 2017).

The data included in the largest report on MCL patients who relapsed after ASCT was obtained between 2000 and 2009, but only 50% of cases had documented exposure to rituximab and HD-AraC before ASCT (Dietrich *et al*, 2014).

Inclusion criteria for this retrospective study of first-relapsed or -refractory MCL patients from 26 centres associated to the Fondazione Italiana Linfomi (FIL) were: (i) upfront treatment with intensive regimens including rituximab and HD-AraC, defined as cytarabine with a single dose >1 g/m^2; (ii) MCL diagnosed between 1 January 2007 and 31 June 2016. Upfront regimens were stratified into three categories: high dose sequential therapy followed by ASCT (Geisler *et al*, 2008; Magni *et al*, 2009); R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone) alternating with R-DHAP (rituximab, dexamethasone, HD-AraC, cisplatin) followed by ASCT (Hermine *et al*, 2016); R-HyperCVAD/MTXHDAC (rituximab, hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone, high-dose methotrexate/cytarabine) followed by

Table I. Clinical and pathological characteristics of 188 relapsed or refractory patients with MCL, classified by time to disease relapse or progression (early *versus* late POD) from the FIL series. The characteristics of the validation set are included in the last column.

Characteristic	All patients n = 188	Early POD n = 90	Late POD n = 98	P value	MCL Younger Validation Set n = 93
Median Age, years (range)	57 (35–68)	58 (35–67)	57 (35–68)	0·95	56 (33–65)
<60 years	117 (62%)	56 (62%)	61 (62%)	0·99	63 (68%)
Gender: Male	143 (76%)	67 (74%)	76 (77%)	0·61	78 (84%)
Stage: IV	168 (89%)	81 (90%)	87 (89%)	0·89	78 (84%)
B symptoms: Yes	61 (32%)	39 (43%)	22 (22%)	**0·002**	40 (43%)
Bone marrow biopsy: Positive	155/183 (85%)	76/87 (87%)	79/96 (82%)	0·34	75 (81%)
MIPI score					
Low	63 (34%)	24 (27%)	39 (40%)	0·13	46 (49%)
Intermediate	56 (30%)	28 (31%)	28 (28%)		27 (29%)
High	69 (37%)	38 (42%)	31 (32%)		20 (22%)
Ki-67 expression: ≥30%	73/141 (52%)	51/72 (71%)	22/69 (32%)	**0·0001**	16/44 (36%)
Morphological variants					
Classical	134/171 (79%)	54/79 (68%)	80/92 (87%)	**0·01**	51/58 (88%)
Pleomorphic	9/171 (5%)	6/79 (7%)	3/92 (3%)		3/58 (5%)
Blastoid	28/171 (16%)	19/79 (24%)	9/92 (10%)		4/58 (7%)
Induction therapy					
HyperCVAD/MTXHDAC	49 (26%)	21 (23%)	28 (29%)	0·51	0 (0%)
R-CHOP/DHAP + ASCT	40 (21%)	22 (25%)	18 (18%)		93 (100%)
Nordic/R-HDS	99 (53%)	47 (52%)	52 (53%)		0 (0%)

Bold indicates significant values.

Mann–Whitney test was adopted for comparing continuous variables; Chi-square test was used for nominal variables.

MIPI high *versus* others P = 0·13; Blastoids *versus* others P = 0·01.

ASCT, autologous stem cell transplantation; R-hyperCVAD/MTXHDAC, rituximab, hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone, high-dose methotrexate/cytarabine; MCL, mantle cell lymphoma; MIPI, Mantle cell lymphoma International Prognostic Index; POD, progression of disease; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; R-DHAP, rituximab, dexamethasone, high-dose cytarabine, cisplatin.

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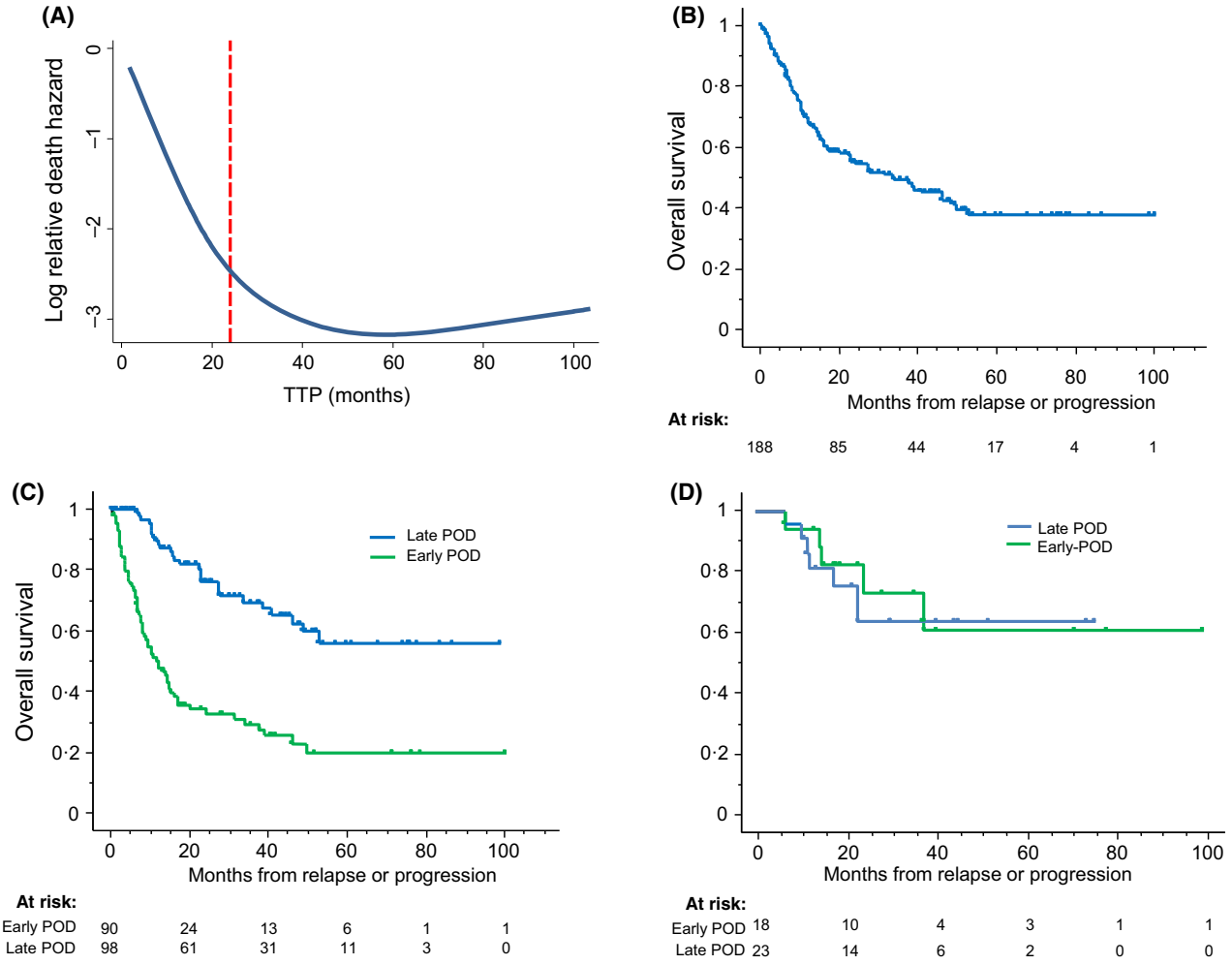

Fig 1. (A) Analysis of 188 patients with mantle cell lymphoma experiencing first relapse or progression of disease (POD). Hazard model showing the relationship between risk of death (Log relative hazard) and time to first relapse or progression (TTP). The vertical dotted line is allocated at the 24 months cut-off. (B) Overall survival from time of POD (OS-2) for all 188 included patients. (C) OS-2 according to POD (early POD *versus* late POD, $P < 0{\cdot}0001$). (D) OS-2 in 41 patients that received allogeneic stem cell transplantation (AlloSCT) at any time during study follow-up. Patients with late POD that had AlloSCT ($n = 23$) had similar OS-2 compared to patients with early POD receiving AlloSCT ($n = 18$, $P = 0{\cdot}72$). [Colour figure can be viewed at wileyonlinelibrary.com]

ASCT at the discretion of the treatment physician (Romaguera *et al*, 2010).

Progression of disease (POD) included primary refractory disease, defined as no response or progression during front-line therapy, and relapsed MCL, defined as relapse after achieving partial or complete remission at the end of induction therapy. Primary outcome was overall survival from POD (OS-2), defined as time from POD until death due to any cause. The European MCL Network randomized, phase 3, MCL Younger trial (Hermine *et al*, 2016) was used for independent validation of our findings (Data S1).

We modelled the relationship between time to POD (TTP) and risk of death using a restricted cubic splines transformation in a Cox proportional hazards model. The curve slope (Fig 1A) showed an approximately linear association within 24 months from MCL diagnosis, while it became flat thereafter, with a point of inflection located around 24 months. Based on this trend, patients were grouped as POD within 24 months of lymphoma diagnosis (early POD group), and those with POD after 24 months of lymphoma diagnosis (late POD group). The 24-month cut-off point approximated the median TTP of recruited patients (25 months, range 2–104). Of the 188 evaluable patients, 90 (48%) had early POD and 98 (52%) had late POD. Patient characteristics are noted in Table I.

Median follow-up time from POD was 30 months (range 3–100), and median OS-2 was 34 months (95% confidence interval [CI], 22–49, Fig 1B). Median OS-2 in the early POD group was 12 months (95% CI, 5–17), while it was not reached for late POD patients (5-year OS-2 55%, 95% CI, 46–62, Fig 1C, logrank $P < 0{\cdot}0001$). Multivariable Cox regression analysis associated early POD with markedly reduced OS-2, with a hazard ratio (HR) of 3·90 (95% CI, 2·16–7·06), being the most powerful factor associated with

an elevated risk of death after adjustment for MCL International Prognostic Index (MIPI) score, Ki-67 expression, combined MIPI, morphological variants and presence of B-symptoms. Subgroup analyses of patients receiving different initial therapy demonstrated similar patterns in the peak hazard of death. Patients refractory to induction therapy (n = 24) had a similar OS-2 (median 6·4 months) to responsive patients that relapsed within 12 months (n = 15; median 7·9 months; P = 0·52). The OS-2 curve and the multivariate analysis results for the 188 patients grouped according to TTP with different cut-offs (0–12, 12–24, >24 months), and the HR associated to different cut-offs (HR of 8·29, 2·39, 1, respectively) are reported in Fig S1.

Forty-one patients (22%) underwent AlloSCT, of whom 28 (68%) were transplanted in second remission and 13 (32%) in third remission or later. AlloSCT had a favourable significant impact on survival (HR = 0·45, 95% CI: 0·24–0·84; P = 0·012), and a significant effect modification of AlloSCT according to POD time was detected ($P_{interaction}$ = 0·012). When we censored patients receiving AlloSCT at the time of transplant in an exploratory analysis, early POD was still the strongest independent variable associated with shorter OS-2 (HR = 3·98, 95% CI: 2·05–7·41; P < 0·0001, Data S2, Table SI). The 18 early POD patients that received AlloSCT, either in second (n = 10) or later (n = 8) remission, had similar OS-2 to patients with late POD that received AlloSCT (HR = 0·81, 95% CI: 0·25–2·56, P = 0·72, Fig 1D).

For the 93 patients in the validation set, median OS-2 was 10 months (95% CI, 6–13). Results from the Cox model confirmed that patients with early POD had an increased risk of death (HR 2·83; 95% CI, 1·66–4·82, P = 0·0001, Data S1, Table SII and SIII). Median OS-2 of the patients with late POD was shorter in the validation cohort than the FIL series (33 months; 95% CI, 13–55, Fig S2), which may reflect the more frequent use of recently developed second line therapies in the FIL series (i.e. ibrutinib or bendamustine-based combinations, such as R-BAC [rituximab, bendamustine, cytarabine] in 69% of patients), as compared to the validation set.

Overall, there is a clear need to identify biological subsets that can be defined prospectively along with associated expected outcomes, such as *TP53* mutations or aberrations (Eskelund *et al*, 2017), which were not investigated in the present study. Given that the expected median survival for younger patients with MCL exceeds 10 years, POD within 2 years of diagnosis identifies a population of patients who have remarkably poor outcomes, irrespective of the prognostic information obtained at diagnosis or induction regimen administered. This newly defined high-risk group of patients represents a distinct population in whom further study is warranted in both directed prospective clinical trials of MCL biology and treatment, including AlloSCT. Likewise, the observation that patients with relapse beyond 2 years have prolonged survival expectation in the modern treatment era seems of great importance in the clinical management of patients with MCL.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Fig S1. (A) OS-2 curve for the 188 patients divided according to TTP with different cut-offs (0–12, 12–24, >24 months); (B) Cox Model for OS-2 according to TTP with different cut-offs.

Fig S2. (A) Overall survival from time of POD (OS-2) for the 93 patients of the validation set (HDAraC group of the MCL Younger trial). (B) OS-2 according to time to POD (early POD *versus* late POD, $P < 0.0001$) in the validation set.

Data S1. Validation of the prognostic effect of time to first treatment failure in mantle cell lymphoma patients refractory to or relapsing after high-dose-cytarabine-containing treatment.

Data S2. List of regimens used as second line treatment.

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