Myeloma before the age of 40: a French retrospective studyRunning title: Myeloma before the age of 40

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Avoir un myélome avant 40 ans : une étude rétrospective francophone

myeloma, international staging system
Myélome, international staging system (ISS)

Abstract

Myeloma is rarely diagnosed at a young age, with fewer than 2% of patients being diagnosed before the age of 40. The characteristics and outcome of this particular population are poorly understood. In this article, we present 214 patients who were 40 years of age or younger at the time of diagnosis of myeloma and related conditions in the 2000s. Of these, 189 had symptomatic myeloma, and their baseline characteristics were broadly similar to those of older patients, except for a higher proportion with a poor prognostic ISS score (ISS-1). In total, 90% received intensified therapy followed by first-line autologous stem cell transplantation, and nearly 25% received an allograft, mainly on first or second relapse. With a median follow-up of 76 months, the estimated median survival was 14.5 years. At five years, overall survival was 84%. Based on multivariate analysis, a high ISS score (ISS-3; HR = 2.14;

Résumé

Le myélome est rarement diagnostiqué très jeune, et moins de 2 % des patients ont moins de 40 ans. Les caractéristiques et le devenir de cette population particulière sont méconnus. Nous présentons ici 214 patients qui avaient 40 ans ou moins au moment du diagnostic de myélome et pathologies apparentées, dans les années 2000. Parmi ceux-ci, 189 présentaient un myélome symptomatique, et leurs caractéristiques initiales étaient globalement identiques à celles de patients plus âgés, si ce n'est une proportion plus élevée de score pronostique ISS (pour *international staging system)* faible (ISS-1); 90 % ont bénéficié d'une intensification thérapeutique suivie d'une autogreffe de cellules souches en première ligne, et près de 25 % une allogreffe principalement a la première ou la seconde rechute. Avec un suivi médian de 76 mois, la survie médiane estimée était de 14,5 ans. A cinq ans, la

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p = 0.03), unfavourable cytogenetics (HR = 4.54; $p < 0.0001$), bone lesions (HR = 3.95; p = 0.01), or disease progression (HR = 12.78; $p < 0.0001$) conferred a shorter survival. Given the low risk of death in the general population of the same age, the relative survival of these patients was relatively close to overall survival (83%), with a 70-fold increased risk of mortality despite their prolonged survival.

survie globale était de 84 %. En analyse multivariée, il s'avère qu'un score ISS élevé (ISS-3; *hazard ratio* [HR] = 2,14; p = 0,03), une cytogénétique défavorable (HR = 4,54; p < 0,0001), des lésions osseuses (HR = 3,95; p = 0,01), ou une progression de la maladie (HR = 12,78; p < 0,0001) conféraient une survie plus courte. Compte tenu du faible risque de décès dans la population générale du même âge, la survie relative de ces patients était relativement proche de la survie globale (83 %), avec un surrisque de mortalité 70 fois plus élevé malgré leur survie prolongée.

Multiple myeloma (MM) is a haematological malignancy usually affecting patients in their 70 s [1]. Few patients are diagnosed at a very young age and fewer than 2% are under the age of 40 [2]. In the literature, only a few small old series have been reported concerning this specific population with sparse data, especially regarding prognostic data. The characteristics of the disease and the outcome of these young patients remain unknown [3-8]. The prognosis of the disease has improved considerably over the years, largely due to the emergence of new drugs with standardised treatment protocols. However, there are no recommendations for this particularly young population, and the use of allografts remains controversial [9, 10]. In this paper, we present a large series of French and Belgian patients with myeloma diagnosed before the age of 40 and treated from the 2000s onwards. We report their initial characteristics, therapeutic management and outcome, and attempt to define prognostic factors.

Patients and methods

Identification of patients

Patients were selected from the French cytogenetic database of the *Intergroupe Francophone du Myélome* (IFM, Prof. H. Avet-Loiseau, Oncopôle Toulouse) between January 2000 and December 2015. In total, 214 patients diagnosed with myeloma between the ages of 18 and 40 years inclusive were identified. Patients with isolated plasmacytoma, primary plasma cell leukaemia (PCL) and indolent myeloma (IMM) were included in the descriptive study (but excluded from the survival analysis), but patients with monoclonal gammopathy of undetermined significance (MGUS) and AL amyloidosis were not included.

Initial clinical and biological data as well as treatment, follow-up and outcome were then extracted directly from the patients' source records.

Patients' compliance with the use of their clinical and biological data was registered at the time of their inclusion in the IFM database. This database has been declared to the Commission Nationale Informatique des Libertés (No. DR-2017-344).

Statistical analysis

For the descriptive analysis, we collected demographic, clinical, and biological data, and recorded treatments received, relapses and survival for each patient. Treatment responses were collected according to the International Myeloma Working Group (IMWG) criteria [11]. Survival analyses were performed only for patients with symptomatic myeloma, and were performed according to standard statistical methods.

The expected and relative mortality of patients was matched according to age and sex with tables available for the French population in the American

(Human Mortality Database, Berkeley) and German (Max Planck Institute for Demographic Research) databases [12, 13].

Results

We were able to identify 214 patients from 38 French and Belgian IFM centres. Of these, 189 patients had symptomatic myeloma, nine had primary plasma cell leukaemia, 10 had indolent myeloma, four had isolated plasmacytoma and two had myeloma complicated by immunoglobulin deposition disease (Randall disease). Almost 50% were diagnosed between 2011 and 2015. The median age at diagnosis was 37 years (range: 18–40 years) and 67% were male. The main clinical data are presented in *table 1*. Nineteen of these patients had a known history of MGUS. The criteria for treatment of myeloma were 75% bone lesions, 35% anaemia, 17% renal failure and 12.8% hypercalcaemia. The ISS prognostic score was predominantly low: 52.4% ISS-1, 27.5% ISS-2 and 20.1% ISS-3. Cytogenetic study data were available for 88% of patients: more than half had cytogenetic abnormalities, 18% of which had a poor prognosis (presence of a 17p deletion or t [4;14] translocation).

Treatments

The type of first-line treatment depended mainly on the time of diagnosis of the disease. Two-thirds of patients had received treatment with a proteasome inhibitor (bortezomib) as first-line therapy; as a triplet therapy with an immunomodulator (IMiD, thalidomide or lenalidomide) plus dexamethasone in 36.6% (VTD or VRD), or with dexamethasone alone (VD), an anthracycline (PAD) or an alkylating agent (VCD) in 30% of cases. It should be noted that 25% of patients received neither bortezomib nor IMiD as first-line therapy. Ninety-three percent of patients received intensive treatment followed by peripheral stem cell autotransplantation (HDM/ASCT) as first line or at relapse. Finally, 46 patients received an allogeneic stem cell transplant, which was first-line in three; 71% at or after the first relapse, of whom six had PCL.

Responses and outlook

The overall response rate (at least partial response) was 95% for first line, of whom 72% had at least a very good partial response (VGPR). These results are summarised in *table 2*. The median survival was 76 months (IQR 1–3: 36–54); follow-up data were available for 182 of 189 patients with symptomatic myeloma. The estimated median survival was 175 months (IQR 1–3 was not reached in 121), resulting in an estimated median survival at five and 10 years of 84% and 59%, respectively (*figure 1*). At five years, relative survival (RS) was 83% (95% CI: 78–89) with a standardised mortality ratio of 69.9 (95% CI: 52.7–91.1), meaning that a patient diagnosed with myeloma before the age of 40 had a 70-fold higher mortality risk compared to individuals of the general population.

Prognostic factors for response and survival

Response rates to the first line of treatment were not dependent on the type of treatment or cytogenetic abnormalities. Similarly, the type of first-line treatment did not influence survival, as overall survival was identical for those who received an IMiD or proteasome inhibitor and those who did not (*table 3*).

Based on univariate analysis, the presence of bone damage (hazard ratio [HR] = 3.15; 95% CI: 1.37–9.13; p = 0.01), anaemia (HR = 2.0.7; 95% CI: 1.19–3.60; p = 0.009), a high prognostic score (ISS-3: HR= 2.63; 95% CI: 1.25–5.41; p = 0.009 and ISS-2 HR = 1.84; 95% CI: 0.89–3.74; p = 0.09; compared to ISS-1) and poor prognostic cytogenetics (HR = 2.75; 95% CI: 1.53–4.93; $p < 0.001$) negatively

Table 1

Clinical and biological features at diagnosis.

Total population, n (%)	214 (100)
Period of diagnosis, n (%)	
• Diagnosis 2000–2005	50 (23.4)
• Diagnosis 2006–2010	60 (28)
• Diagnosis 2011–2015	104 (48.6)
Gender, n (%)	
Male/female	137 (64) / 77 (36)
Median age, years (± SD; min-max)	37.2 / 4.3; 18.6–40.9)
Diagnosis, n (%)	
• Symptomatic MM	189 (88.3)
• LPP	9 (4.2)
• Indolent myeloma	10 (4.7)
• Isolated plasmacytoma	4 (1.9)
• Randall disease	2 (0.9)
Isotype, n (%)	
• Whole immunoglobulin	162 (76)
– IgA	28 (17.3)
– IgG	130 (80.2)
– IgM	1 (0.06)
– IgD	3 (1.9)
• Light chain only	51 (24)
Type of light chain, n (%)	
κ/λ	138 (66) / 71 (34)
Bone lesions, n (%)	149 (75)
Imaging, n (%)*	
• Standard radiology	100 (52.6)
• Scanner	64 (33.7)
• MRI	114 (60)
• PET	27 (14.2)
• None	4 (2.1)
Glomerular filtration rate (GFR, MDRD), n (%)	
• > 60 mL/min/1.73m^2	166 (83)
• < 60 mL/min/1.73m^2	34 (17)
Hypercalcaemia, n (%)	
• > 2.75 mmol/L	25 (12.8)
• < 2.75 mmol/L	170 (87.2)
Proteinuria > 1 g/L, n (%)	34 (22.7)
Albumin level (g/L) median ± SD	39.2 ± 8.2
β2-microglobulinaemia (g/L) median ± SD	2.83 ± 14.5

Cytopenias, n (%)	
• Anaemia (Hb < 10 g/dL)	71 (35.1)
• Neutropenia (PNN < 1.5 G/L)	9 (4.7)
• Thrombocytopenia (platelets < 100 G/L)	8 (4)
ISS score, n (%)	
• 1	99 (52.4)
• 2	52 (27.5)
• 3	38 (20.1)
Cytogenetics, n (%)	
• Unfavourable*	34 (18)
– 1(4;14)	19 (12.2)
– del(17p)	17 (12.1)
• Other, including:	65 (34.4)
– (11;14)	9 (25.7)
– (14;16)	1 (2.5)
– +1q	17 (30.4)
– del1p32[$]	8 (17.4)

*two patients had t(4;14) and del(17p)
[#]associated with unfavourable cytogenetics in five patients
[$]associated with unfavourable cytogenetics in two patients; associated with +1q in five patients

Table 2

First-line treatments.

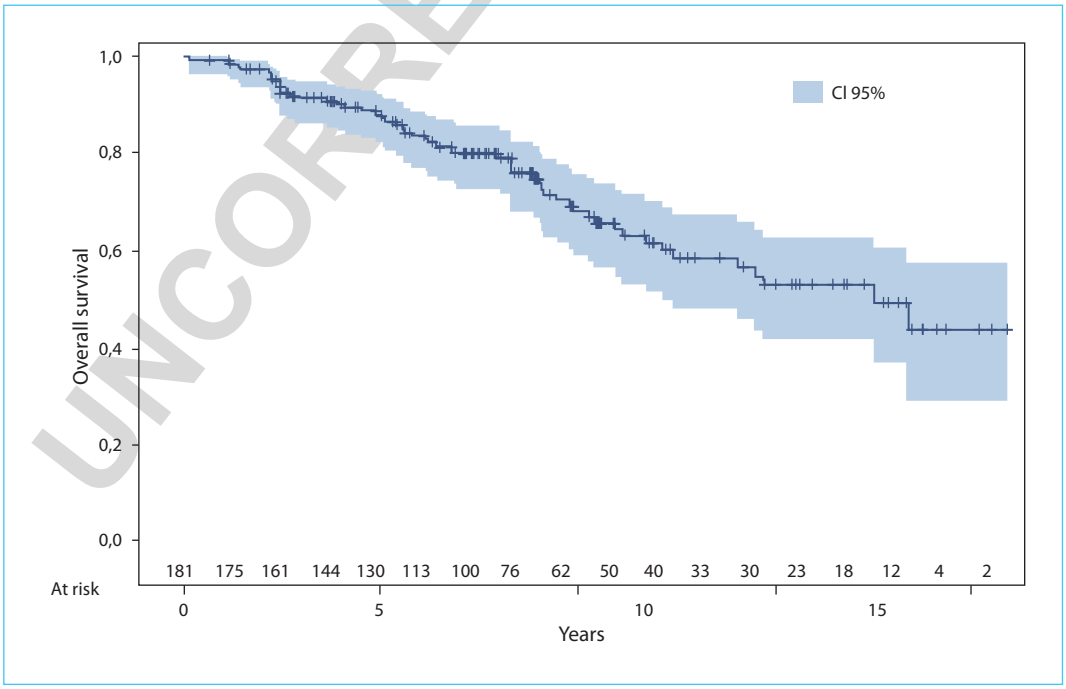
Total population, n (%)	214 (100)
Induction treatment, n (%)	
• VD/VCD/PAD	64 (30)
• VTD/VRD	78 (36.6)
• VAD/DCEP	55 (25.8)
• Other (Thal + Dex)	3 (1.4)
• None (except radiotherapy)	13 (6.1)
Autograft (ASCT), n (%)	184 (93)
• Single	142 (77)
• Tandem	42 (23)
Consolidation OR maintenance, n (%)	108 (58.7)
Consolidation AND maintenance, n (%)	29 (15.8)
IP OR IMiD as first-line, n (%)	159 (79.9)
IP + IMiD as first-line, n (%)	104 (52.3)
Allograft, n (%)	46 (24.9)
• First-line	13 (28.9)
• Second-line	22 (48.9)
• >Second-line	10 (22.2)

Response at the end of first-line*, n (%)	
• CR	73 (38.2)
• VGPR	64 (33.5)
• VGPR	137 (71.7)
• PR	46 (24.1)
• SD	4 (2.1)
• PD	4 (2.1)

VD = bortezomib + dexamethasone, VCD = bortezomib + cyclophosphamide + dexamethasone, PAD = bortezomib + doxorubicin + dexamethasone, VTD = bortezomib + thalidomide + dexamethasone VRD = bortezomib + lenalidomide + dexamethasone, VAD = vincristine + doxorubicin + dexamethasone, DCEP = cisplatin + cyclophosphamide + etoposide + dexamethasone
* Haematological response according to IMWG criteria,
CR = complete response, VGPR = very good partial response, PR = partial response, SD = stable disease, PD = progressive disease.

influenced survival. Based on multivariate analysis, the presence of bone lesions (HR = 3.95; 95% CI: 1.37–11.38; p = 0.011), ISS-3 (HR = 2.14; 95% CI: 1.07–4.27; p = 0.03) and poor prognostic cytogenetics (HR = 4.54; 95% CI: 2.26–9.11; $p < 0.0001$) were independent factors for poorer survival (*table 4*). As cytogenetic prognostic factors have evolved over time, we also analysed a subgroup of patients who had more complete cytogenetics based on NGS; inclusion of t(14;16), 1q amplification or gain or 1p32 deletion, according to the definition of high-risk groups, remained an adverse prognostic factor.

FIGURE 1



Estimated overall patient survival.

Table 3

Overall survival based on univariate analysis.

Variable	Deaths / N	HR:	95% CI	*p*-value
Age (years)				
• < 30	2 / 19	1.00		
• 30–35 • > 35	13 / 38 36 / 121	2.04 1.89	0.66–8.86 0.68–7.85	0.26 0.29
Previous MGUS				
• No	46 / 160	1.00		
• Yes	1 / 12	0.27	0.01–1.22	0.19
Isotype				
• IgG	36 / 110	1.00		
• IgA	7 / 23	1.19	0.54–2.37	0.63
MM light chain				
• No	42 / 133	1.00		
• Yes	8 / 43	0.59	0.27–1.15	0.15
Bone lesions				
• No	6 / 36	1.00		
• Yes	41 / 133	3.15	1.37–9.13	0.01*
Hypercalcemia				
• < 2.75 mmol/L	41 / 146	1.00		
• > 2.75 mmol/L	7 / 18	1.82	0.79–3.66	0.12
GFR (mL/min)				
• > 60 • < 60	38 / 141 10 / 28	1.00 1.57	0.74–3.02	0.20
Proteinuria > 1 g/L				
• No	25 / 95	1.00		
• Yes	8 / 29	1.13	0.52–2.27	0.73
Anaemia				
• No • Yes	26 / 110 22 / 59	1.00 2.07	1.19–3.60	0.009*
ISS score				
• 1	18 / 87	1.00		
• 2 • 3	13 / 40 12 / 30	1.84 2.63	0.89–3.74 1.25–5.41	0.09* 0.009*

(*Continued*)

Table 3

(*Continued*)

Variable	Deaths / N	HR:	95% CI	*p*-value
Unfavourable cytogenetics				
• No	37 / 152	1.00		
• Yes	14 / 31	2.75	1.53–4.93	< 0.001
First-line treatment				
• VAD/DCEP	24 / 49	1.00		
• VD/VCD/PAD • VTD/VRD	15 / 53 11 / 73	0.85 0.72	0.43–1.62 0.33–1.48	0.61 0.37

^Variables selected for multivariate analysis.
VAD = vincristine + doxorubicin + dexamethasone, DCEP = cisplatin + cyclophosphamide + etoposide + dexamethasone, VD = bortezomib + dexamethasone, VCD = bortezomib + cyclophosphamide + dexamethasone PAD = bortezomib + doxorubicin + dexamethasone, VTD = bortezomib + thalidomide + dexamethasone, VRD = bortezomib + lenalidomide + dexamethasone. GFR = glomerular filtration rate.

Finally, among the predefined time-dependent variables, only the date of progression (HR = 13.2; 95% CI: 5.6–37.3; $p < 0.0001$) had a negative impact on overall survival (*table 5*).

Discussion

In this article, we present one of the largest series of patients who were diagnosed with myeloma before the age of 40; the characteristics and fate of this particularly young population remain poorly known. In these patients, the characteristics of the disease differed only slightly from those of older patients, except for a higher proportion of low ISS scores (ISS-1 in 50% compared with fewer than 30% usually); this has been reported in other studies and could explain, at least in part, the relatively long survival period of these very young patients [4, 5]. The five-year survival of our patients was 84% with an estimated median survival of 14.5 years, substantially longer than the 8–9-year survival usually reported for populations under 65 years of age [1, 14]. We also estimated the RS of this population and compared it to that of the general population of the same age group; the two were

Table 4

Overall survival based on multivariate analysis.

Variable	HR:	95% CI		*p*-value
ISS3 versus ISS1	2.14	1.07	4.27	0.03
Unfavourable cytogenetics	4.54	2.26	9.11	< 0.0001
Bone lesions	3.95	1.37	11.38	0.01

All variables reaching statistical significance at $p < 0.1$ were included in the multivariate analysis.

Table 5

Overall survival estimated for time-dependent variables.

		HR:	95% CI		*p*-value
Univariate variable	Complete response achieved Progression of the disease Allograft	0.745 13.227 2.351	0.258 5.589 1.249	1.705 37.252 4.243	0.53 < 0.0001 0.006
Multivariate variable	Allograft Progression of the disease	1.781 12.278	0.953 5.171	3.186 34.652	0.06 < 0.0001

ultimately fairly close since the RS was 83% (95% CI: 78-89), considering the low risk of death associated with the absence of MM. However, the standardised mortality rate (SMR) was 70-fold higher than that expected for a population under 40 years of age, indicating a very high excess risk of myeloma-related mortality. The impact of new drugs on survival remains under debate. For example, according to the Swedish registry data, there was no improvement in survival for patients under 65 years of age between the periods 2008–2010 and 2011–2015 [1, 15]. In contrast, five and 10-year survival doubled for patients under 40 years of age treated before 1993 and after 2003 in the US registries, with the exception of Hispanic patients [16].

Only ISS-3, the presence of bone lesions and unfavourable cytogenetics influenced the overall survival of our patients, in contrast to first-line treatment. Some treatments reported in our series are no longer used, and triplet treatments combining a proteasome inhibitor, IMiD and dexamethasone are now proposed before autotransplantation and systematically as consolidation for these young patients, as well as a maintenance treatment with lenalidomide. Finally, there is no doubt that the recent addition of an anti-CD38 antibody to this therapeutic arsenal will considerably improve the survival of this young population [17]. The fact that progression-free survival after a first-line treatment is short while overall survival is relatively long may perhaps be explained by the possibility that several lines of treatment can be offered to this very young population, including a second autograft upon relapse, or even an allograft. While the role and benefit of allogeneic transplantation in myeloma remains highly controversial, it should be noted that more than 20% of our patients have been offered such a treatment. This is certainly due to the long inclusion period and the limited therapeutic armamentarium in the early 2000s, and perhaps also to the hope of a cure for myeloma using allografts for this very young population.

On the other hand, only date of progression negatively affected overall survival among the time-dependent variables, in contrast to allografts or achieving complete remission. However, it is now clearly established that achieving complete remission and especially undetectable minimal residual disease (UMRD) after first-line treatment is a major prognostic factor for longer survival [18, 21]. In this retrospective study, the extent of response was difficult to estimate beyond the very high VGPR, particularly in the absence of systematic myelogram and bone marrow phenotyping, and MRD data were not available. We believe that this certainly underestimates the importance of the extent of response to first-line treatment in these young patients.

Conclusion

Based on this retrospective multicentre study of a large number of patients, we show that the disease characteristics at diagnosis were similar between those aged

40 years or younger and those of older patients. These very young patients had a relatively long overall survival period despite a short progression-free survival period after first-line treatment, but a significantly increased myeloma-related mortality compared to the general population. We also confirm that high-risk cytogenetics remains a poor prognostic factor. The patients presented here were diagnosed before 2015 and therefore did not benefit from the new therapeutic strategies, including, in particular, an anti-CD38 monoclonal antibody as first-line treatment, which, combined with proteasome inhibitors and IMiDs, significantly increases patient survival [17]. In the very near future, patients will probably benefit from new immunotherapies such as chimeric antigen receptor T cells (CAR-T) or certain bispecific antibodies [22-24]. A cure for myeloma, at least for a number of patients, and probably for the youngest among them, may no longer be just a dream.

Strengths

- Inclusion period: 2000–2015; median follow-up: 6.3 years; estimated median overall survival: 14.5 years.
- Poor cytogenetics and ISS-3 score remain poor prognostic factors.
- Prognosis is likely to improve in the coming years with the systematic introduction of monoclonal antibodies (anti-CD38) for diagnosis and the interest in new immunotherapies (bispecific antibodies and chimeric antigen receptor T cells [CAR-T]).

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Question à l'auteur

Q1 Please check and confirm.