Age is a prognostic factor even among patients with multiple myeloma younger than 66 years treated with high-dose melphalan: the IFM experience on 2316 patients

Marie-Lorraine Chretien,[1,2]* Benjamin Hebraud,[1]* Valérie Cances-Lauwers,[3] Cyrille Hulin,[4] Gerald Marit,[5] Xavier Leleu,[6] Lionel Karlin,[7] Murielle Roussel,[8] Anne-Marie Stoppa,[9] Francois Guilhot,[10] Thierry Lamy,[11] Laurent Garderet,[12] Brigitte Pegourie,[13] Mamoun Dib,[14] Catherine Sebban,[15] Pascal Lenain,[16] Sabine Brechignac,[17] Bruno Royer,[18] Marc Wetterwald,[19] Laurence Legros,[20] Frédérique Orsini-Piocelle,[21] Laurent Voillat,[22] Xavier Delbrel,[23] Denis Caillot,[2] Margaret Macro,[24] Thierry Facon,[6] Michel Attal,[8] Philippe Moreau,[25] Hervé Avet-Loiseau,[1] and Jill Corre[1]

[1]Unité de Génomique du Myélome, University Hospital; CRCT, INSERM U 1037; Université Paul Sabatier, Toulouse; [2]Department of Hematology, University Hospital, Dijon; [3]Service d'Epidémiologie, CHU Toulouse; [4]Department of Hematology, University Hospital, Nancy; [5]Department of Hematology, University Hospital, Bordeaux; [6]Department of Hematology, University Hospital, Lille; [7]Department of Hematology, University Hospital, Lyon; [8]Department of Hematology, University Hospital, Toulouse; [9]Department of Hematology, Institut Paoli Calmette, Marseille; [10]CIC Inserm 0802, Centre Hospitalier Universitaire, Poitiers; [11]Department of Hematology, University Hospital, Rennes; [12]Department of Hematology, University Hospital, St-Antoine, Paris; [13]Department of Hematology, University Hospital, Grenoble; [14]Department of Hematology, University Hospital, Angers; [15]Department of Hematology, Centre Léon Bérard, Lyon; [16]Department of Hematology, Centre Becquerel, Rouen; [17]Department of Hematology, University Hospital, Bobigny; [18]Department of Hematology, University Hospital, Amiens; [19]Department of Hematology, Departmental Hospital, Dunkerque; [20]Department of Hematology, University Hospital, Nice; [21]Department of Hematology, Departmental Hospital, Annecy; [22]Department of Hematology, Departmental Hospital, Chalon; [23]Department of Hematology, Departmental Hospital, Pau; [24]Department of Hematology, University Hospital, Caen; and [25]Department of Hematology, University Hospital, Nantes, France

*MLC and BH contributed equally to this work.

ABSTRACT

Age is a strong prognostic factor in multiple myeloma. The overall survival is shorter in patients older than 66 years, and even shorter in those older than 75 years. Whether age is also a prognostic parameter in patients younger than 66 years treated homogeneously with intensive approaches is unknown. To address this issue, we retrospectively analyzed a series of 2316 patients treated homogeneously with 3-4 cycles of induction chemotherapy followed by a high-dose melphalan course, without any consolidation or maintenance. We show that patients older than 60 years have a statistically significant shorter overall survival. The analysis of prognostic parameters did not show a higher incidence of high-risk cytogenetics, but a higher incidence of International Staging System (ISS) stages 2 and 3, mainly due to higher β2-microglobulin levels. This study is the first to demonstrate the impact of age in the outcome of 'young' patients with multiple myeloma, and suggests that this parameter should be included in the stratification factors for future prospective clinical trials.

Introduction

Age is a prognostic factor observed in every kind of cancers. Many factors can explain this finding: more co-morbidities in elderly, poorer renal and liver functions affecting the metabolism of anticancer drugs, but also more adverse prognostic factor sometimes observed in older patients (like Ph1-positivity in acute lymphoblastic leukemias). In multiple myeloma (MM), age is also a strong prognostic parameter. Indeed, the median overall survival (OS) of patients older than 65 years of age is currently approximately 4-6 years, whereas it is around ten years for younger patients. Apart from co-morbidities (that are of course more frequent in elderly patients), this important difference in survival is mainly due to the treatment approaches used in these two populations. Patients under 66 years of age are treated with a much more aggressive approach including triplet induction, high-dose melphalan with autologous stem cell rescue, and consolidation, than older patients who are not able to tolerate the high-dose procedure. Regarding other prognostic factors, we previously reported that elderly patients do not present a higher incidence of adverse cytogenetic abnormalities.[1236]

Whether age could also affect the outcome of young patients (< 66 years) is an unresolved question. Only one report suggests that age could impair the outcome.[2] In order to address these questions, we retrospectively analyzed a large series of 2316 patients diagnosed with MM before their 66th birthday, all treated with high-dose melphalan, and systematically analyzed at diagnosis for the two main adverse chromosomal abnormalities, i.e. t(4;14) and del(17p).

Methods

We searched the Intergroupe Francophone du Myélome (IFM) database for patients younger than 66 years of age treated with high-dose melphalan who had benefited from a cytogenetic evaluation. Patients were diagnosed between 1999 and 2010 in one of the IFM centers. For

 doi:10.3324/haematol.2013.098608
Manuscript received on September 24, 2013. Manuscript accepted on April 7, 2014.
Correspondence: avet-loiseau.h@chu-toulouse.fr or corre.j@chu-toulouse.fr

all the patients, a bone marrow sample was shipped overnight to a central laboratory. Upon receipt, malignant plasma cells were purified for fluorescence *in situ* hybridization (FISH) analysis, as previously described.[3] For the large majority of these patients, blood was also sent, enabling a centralized assessment of the β2-microglobulin (β2m) level. To be enrolled, patients must have received an induction therapy and 1 or 2 courses of high-dose melphalan. We excluded patients who had received a consolidation or maintenance regimen, and patients who had received an allogeneic transplant.

Results

We found 2316 patients responding to these criteria. The median age was 57 years (range 23-65), with 65% under 60 years; 56% were males. Approximately half of the patients (1142 patients, 49.3%) received a VAD induction regimen (vincristine-adriamycin-dexamethasone), the other patients (1174 patients, 50.7%) receiving a bortezomib-based induction, combined with dexamethasone +/- thalidomide. This stratification is essentially dependent on the date of diagnosis with a change in 2006-2007 after the results of the IFM 2005-01 trial had been made available.[4] All the patients received a single or double high-dose melphalan course. No patient received either a consolidation regimen, or a maintenance therapy. β2m was available for 92% of the patients; median value was 3.3 mg/L (range 0.6-55.3). The International Staging System (ISS)[5] category was available for 80% of the patients, with respectively 34.7%, 38.3%, and 27% of stage 1, 2 and 3. Out of 2048 patients evaluable for the del(17p) (11.6% had been compromised by technical failure), 171 patients (8.3%) presented a deletion in more than 60% of their plasma cells. Regarding the t(4;14), 2036 patients were evaluable (failure rate 12.1%) and 248 of them were positive for the translocation (12.2%).

Data were then analyzed according to age with a 60-year cut off. More ISS 2 and 3 were observed in the older group, with respectively 37.2%, 37.1% and 25.6% ISS 1, 2 and 3 in the younger patients *versus* 30%, 40.4% and 29.7% in the older group (P<0.007). The statistical difference between these results are mainly due to a higher β2m level in patients older than 60 years, and less frequently to a lower albumin level. Regarding the two chromosomal abnormalities, no incidence difference was observed: 8.2% *versus* 8.5% for del(17p), and 11.6% *versus* 13.3% for t(4;14) (NS).

We also looked at the incidence of these chromosomal abnormalities in particularly young patients, i.e. those under 45 years of age. No difference was observed, with an incidence of del(17p) and t(4;14) of 7.1% and 13.1%, respectively, that showed no significant difference from the other patients.

Patients were then analyzed for overall survival (OS). Median OS was 100 months. Treatment induction did not affect outcome. The risk of death increased linearly with age, with an increased risk of 22% every ten years. With a cut off at 60 years, older patients presented a significantly shorter OS (P=0.003) (Figure 1). In the univariate analysis, other factors associated with outcome (OS) were the ISS, with Hazard Ratios (HR) of 1.41 and 2.45 for ISS 2 and 3 as compared to ISS 1, presence of a del(17p) in more than 60% of the plasma cells (HR=3.47), presence of the t(4;14) (HR=2.60), and a hemoglobin level lower than 10 g/dL (HR=1.75). In the multivariate analysis, age (HR=1.23), ISS 3 (HR=2.04), del(17p) (HR=1.93), and t(4.14 (HR=2.37) were independent prognostic factors.

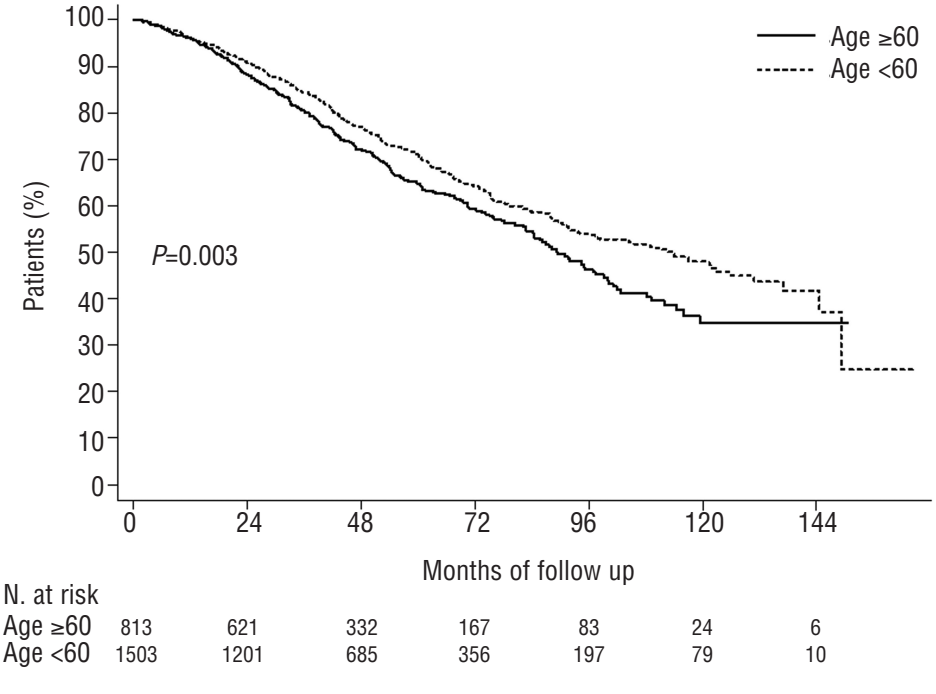

Figure 1. Impact of age (< 60 *vs.* > 60 years) on the overall survival.

Discussion

In MM, it has been known for a long time that age is a strong prognostic factor. Currently, most investigators choose a cut off at 65 years in their design of clinical trials. This cut off is essentially based on the feasibility of high-dose melphalan after this age with more side-effects. Whether this barrier can be increased to 70 years, or even higher for fit patients, is a matter of debate. In elderly patients, age is a known prognostic parameter, especially for very old patients (> 75-80 years).[6] In 'young' patients (< 65 years), few large series has investigated this parameter. One study suggested a better outcome for patients younger than 40 years,[7] but these patients were treated in the 1980s when only melphalan and steroids were available. A more recent retrospective study did analyze patients under 50 years of age.[8] This study showed a better outcome for young patients when treated with standard doses of chemotherapy, but not if treated with high-dose melphalan.

In this series, we analyzed a large number of patients (> 2000) in order to address these questions. Our findings are quite interesting. First, very young patients do not seem to present a characteristic disease. They display similar incidences of high-risk cytogenetic changes, and their outcome is not statistically different to that of patients aged 46-60 years. In the analysis, the prognostic impact of age showed a linear importance of age on the risk of death, with a 22% increase every ten years. This higher risk is especially prominent in patients older than 60 years. This higher risk of death does not seem to be related to cytogenetic factors, with a similar incidence of high-risk markers. The main explanation is related to ISS. We found a significant higher percentage of ISS 2 and 3 stages after 60 years of age. This finding is essentially related to a higher β2m level. The β2m level is mainly related to two factors: i) release from plasma cell surface via shedding; and ii) elimination via renal filtration. A higher production of β2m could be due to a higher tumor burden, or a higher shedding activity. These two hypotheses are rather unlikely in this specific age population. A lower elimination rate is a more likely hypothesis. Even though we did not observe a higher creatinine level in the 60-65 years population (data available for less than half of the patients), it is well known that renal function decreases with age. Whether this observation is true as early as the age of 60 years is unknown, but remains the most likely explanation.

We are not aware of a large study that has analyzed this parameter before. Does it mean that these patients should not be treated with high-dose approaches? Probably not, since in our series the outcome of these patients is quite good (median OS = 89 months). However, we believe that this cut off should be included in the stratification strategies when designing a new trial.

Authorship and Disclosures

Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

References

1. Avet-Loiseau H, Hulin C, Campion L, Rodon P, Marit G, Attal M, et al. Chromosomal abnormalities are major prognostic factors in elderly patients with multiple myeloma. J Clin Oncol. 2013;31(22):2806-9.
2. Lenhoff S, Hjorth M, Westin J, Brinch L, Backstrom B, Karlson K, et al. Impact of age on survival after intensive therapy for multiple myeloma: a population-based study by the Nordic Myeloma Study Group. Br J Haematol. 2006;133(4):389-96.
3. Avet-Loiseau H, Attal M, Moreau P, Charbonnel C, Garban F, Hulin C, et al. Genetic abnormalities and survival in multiple myeloma: the experience of the Intergroupe Francophone du Myélome. Blood. 2007;109(8):3489-95.
4. Moreau P, Avet-Loiseau H, Facon T, Attal M, Tiab M, Hulin C, et al. Bortezomib plus dexamethasone versus reduced-dose bortezomib, thalidomide plus dexamethasone as induction treatment before autologous stem cell transplantation in newly diagnosed multiple myeloma. Blood. 2011;118 (22):5752-8.
5. Greipp PR, San Miguel J, Durie BG, Crowley JJ, Barlogie B, Blade J, et al. International staging system for multiple myeloma. J Clin Oncol. 2005;23(15):3412-20.
6. Bringhen S, Mateos MV, Zweegman S, Larocca A, Falcone AP, Oriol A, et al. Age and organ damage correlate with poor survival in myeloma patients: meta-analysis of 1435 individual patient data from 4 randomized trials. Haematologica. 2013;98(6): 980-7.
7. Bladé J, Kyle RA, Greipp PR. Presenting features and prognosis in 72 patients with multiple myeloma who were younger than 40 years. Br J Haematol. 1996;93(2):345-51.
8. Ludwig H, Durie BG, Bolejack V, Turesson I, Kyle RA, Blade J, et al. Myeloma in patients younger than age 50 years presents with more favorable features and shows better survival: an analysis of 10 549 patients from the International Myeloma Working Group. Blood. 2008;111(8):4039-47.