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Improved survival in multiple myeloma during the 2005–2009 and 2010–2014 periods

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Multiple myeloma (MM) is a B-cell malignancy involving plasma cells. The disease is mainly localized within the bone marrow, leading to bone destruction, anemia, hypercalcemia, and/or renal failure due to monoclonal immunoglobulin precipitation [1]. For a long time, MM has been described as an incurable cancer, even though recent trials with novel drugs have demonstrated projected long survival, suggesting that some patients could currently be considered as cured [2–5]. One of the main characteristics of the disease is the

huge heterogeneity in evolution. Overall survival (OS) extends from a few weeks in ultra-high-risk patients, to more than 15 years in so-called low-risk patients, even though their definition is currently largely unknown. These OS differences are supposed to reflect the extreme molecular heterogeneity observed within the malignant plasma cells. In contrast to non-Hodgkin lymphomas, no subclassification of MM has been described based on the recurrent chromosomal abnormalities, and all the patients receive the same treatments. The only factor dictating treatment is age, defining transplant-eligible (TE) patients, and non-transplant-eligible (NTE) ones. Among the recurrent chromosomal abnormalities, several have been associated with shorter survival, the so-called high-risk features. The International Myeloma Working Group

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(IMWG) identified three high-risk cytogenetic abnormalities: del(17p), t(4;14), and t(14;16), with an incidence of 7–10%, 12–15%, and 3%, respectively [6].

Very few large studies have analyzed the long-term survival of patients with MM [7]. The main reason is that prospective trials are mainly focused on progression-free survival (PFS), with very little attempt to analyze the long-term OS. In order to analyze the survival of patients in “real life,” we decided to analyze a large series of patients treated in France. In order to evaluate potential progress in PFS and OS over time, we focused on two groups of patients, a first one defined by diagnosis between January 1st, 2005 and December 31st, 2009, and a second one defined by diagnosis between January 1st, 2010 and December 31st, 2014.

Within the Intergroupe Francophone du Myélome (IFM), most of the bone marrow samples at the time of diagnosis are sent to a central laboratory for cytogenetic analysis. The medical patient documents are then sent to a single person (HAL) who is in charge of analyzing them and maintaining a database of most biological diagnostic parameters, treatment phases, relapse dates, and survival. After overnight shipment, bone marrow samples are analyzed for at least two chromosomal abnormalities, i.e., del(17p) and t(4;14), as previously described. Patients were included in the analysis on the basis of a signed informed consent, and on availability of medical records for follow up. Patients were divided in two analysis groups, based on the intent to administer high-dose melphalan followed by autologous stem cell transplantation (TE patients), defined by the physicians at the time of diagnosis, or not (NTE patients).

During this 10-year period, adequate data were collected for 4811 patients, 1932 patients during the first period (2005–2009), and 2879 patients in the second one (2010–2014). The increased number of patients collected during the second period is mainly due to more elderly patients being analyzed for cytogenetics in recent times. Patients were diagnosed in a University or local/regional hospital. The repartition based on TE and NTE during these two periods was 1567/365 and 1821/1058, respectively, for 2005–2009 and 2010–2014. Median age for NTE patients was 73 years (range = 43–95) and 58 years (range = 22–74) for TE patients. Median follow-up was 103 months for the 2005–2009 cohort, and 65 months for the 2010–2014 one. Because of small numbers, the impact on OS of high-risk features was analyzed only in the TE cohort. Del(17p) was present in 216 patients, and t(4;14) in 364 patients. Frontline treatment did not significantly change for TE patients over time. In the first period, patients mainly received a bortezomib-based induction with VD (bortezomib–dexamethasone) or VTD (bortezomib–thalidomide–dexamethasone) with no consolidation, while in the second period, patients mainly received a VTD induction with a two-cycle VTD

consolidation (Table 1). For NTE patients, we observed a significant change in frontline treatment, with a switch from MPT (melphalan–prednisone–thalidomide) to MPV (melphalan–prednisone–bortezomib). In the first period, 64% of elderly patients received MPT, whereas in the second period, 66% received MPV.

Looking at PFS separately in the two groups, and in the two periods, interestingly, we did not observe any significant difference between the two groups of patients. For NTE patients in the 2005–2009 and 2010–2014 periods, the median PFS was 25.2 vs. 25.9 months ($p = 0.77$), respectively. For TE patients, the median PFS was 35.3 vs. 37.2 months ($p = 0.09$), respectively (Fig. 1a). In contrast, significant differences in OS were observed between the two groups. For NTE patients, the median OS was 58.8 vs. 83.7 months ($p < 0.0001$), respectively. For TE patients, the median OS was 111 months vs. not reached ($p < 0.0001$), respectively (Fig. 1b).

We then focused our analysis on high-risk patients, i.e., patients with either del(17p) in more than 55% of their plasma cells, or t(4;14). Three hundred and sixty-four patients displayed t(4;14), and two hundred and sixteen patients presented del(17p). For these two high-risk subgroups, no OS difference was observed within each period. For t(4;14) patients in the 2005–2009 and 2010–2014 periods, the median OS was 72.3 vs. 70.4 months ($p = 0.92$), respectively. For del(17p) patients, the median OS was 53.2 vs. 47.4 months ($p = 0.67$), respectively (Fig. 1c).

Very few “real life” studies have been reported over time for patients with MM. We report here the analysis of 4811 patients over a 10-year period. Interestingly, we did not observe any significant PFS difference over time, in both the NTE and TE cohorts. The main changes observed in treatment were a significant switch from MPT to MPV for the NTE patients, and a more systematic use of

Table 1 Type of treatment received as 1st line therapy for the two periods.

Treatment type	2005–2009	2010–2014
MP	67	27
MPT	234	331
MPV	64	700
VAD-MEL200	453	4
VD-MEL200	956	295
VTD-MEL200	133	741
VTD-MEL200-VTD	25	781

MP melphalan–prednisone, MPT melphalan–prednisone–thalidomide, MPV melphalan–prednisone–bortezomib, VAD-MEL200 vincristine–adriamycin–dexamethasone followed by high-dose melphalan, VD-MEL200 bortezomib–dexamethasone followed by high-dose melphalan, VTD-MEL200 bortezomib–thalidomide–dexamethasone followed by high-dose melphalan, VTD-MEL200-VTD bortezomib–thalidomide–dexamethasone followed by high-dose melphalan, and two cycles of bortezomib–thalidomide–dexamethasone consolidation.

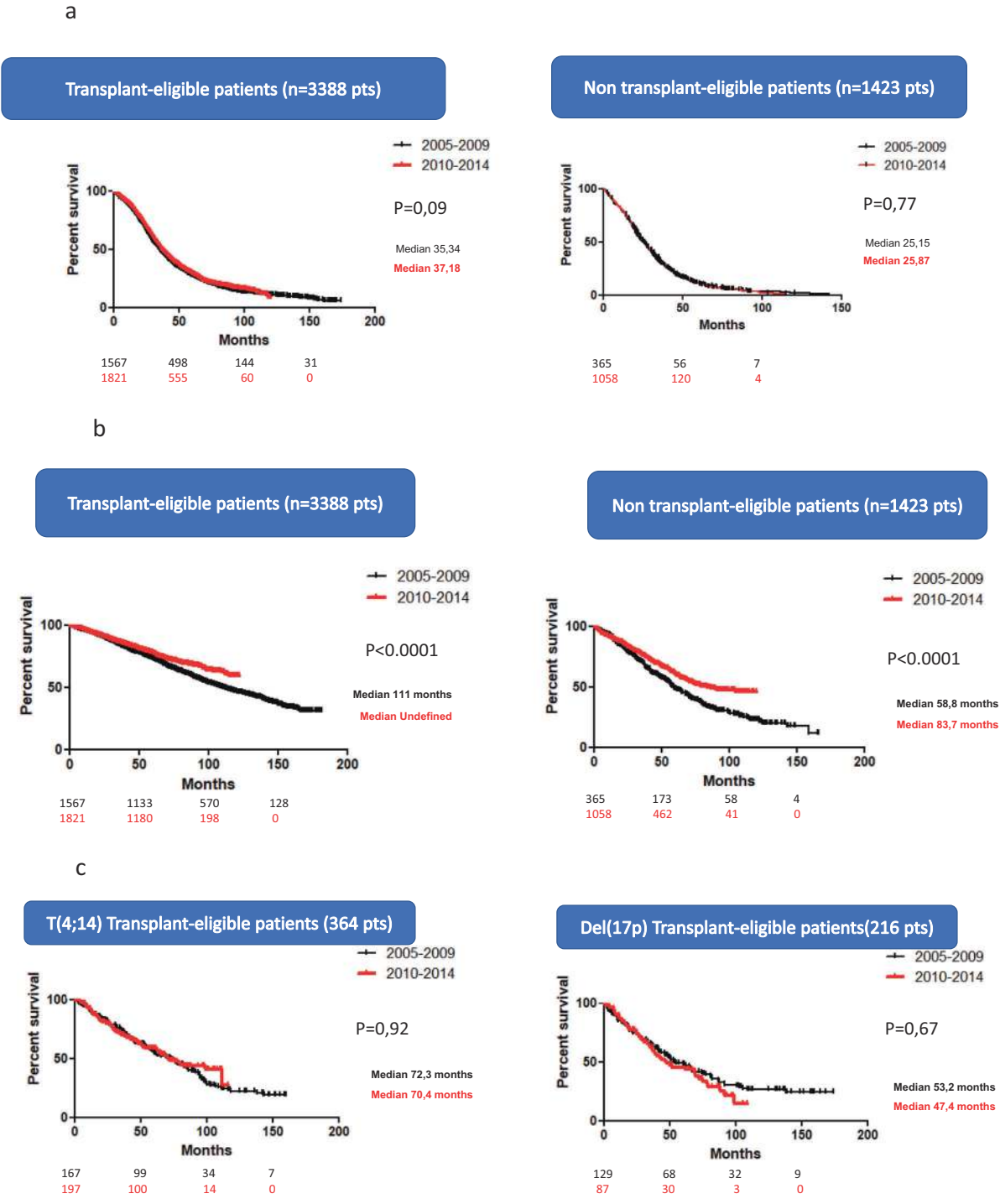


Fig. 1 Comparison of survivals for the two periods (2005-2009 and 2010-2014). a Progression-free survival curves for the two periods (2005-2009 and 2010-2014). b Overall survival curves for the two

periods (2005-2009 and 2010-2014). c Overall survival curves for high-risk transplant-eligible patients for the two periods (2005-2009 and 2010-2014). pts means patients.

consolidation for TE patients. None of these changes have seemed to improve PFS. In contrast, we observed a very significant improvement in OS in both cohorts. This apparent discrepancy highlights the role of subsequent treatments at relapse on OS. Over time, several novel drugs

have been approved for the treatment of MM, such as pomalidomide, carfilzomib, or daratumumab. These drugs are highly efficient and can rescue patients by prolonging OS. Of note, no improvement in OS was observed for high-risk patients in the TE cohort, highlighting a group with a

real unmet medical need. These results suggest that only the so-called standard-risk patients benefit from novel drugs.

Outside of any clinical trial, the PFS and OS for TE and NTE patients were respectively 37.2, 25.9 months, and >10 years and 83.7 months. These results are really impressive, especially for OS. Is it time to talk about cure in MM? The answer is probably “not yet.” For NTE patients, with a median age at diagnosis of 73 years, a 7-year OS leads to 80 years of age, which is at least 5 years less than the general population. For TE patients, the median is not reached, and will probably cross the 10-year threshold. It is probably too early to talk about cure for these young patients, and much longer follow-up will be needed.

How to improve these data? We believe that improvement in OS for all patients will require improvements at all treatment phases. For instance, for TE patients, in the IFM 2009 trial, the median PFS for transplanted patients was 50 months, significantly longer than the 3 years observed in this study [8]. This is probably mainly related to the lenalidomide maintenance phase, which is now the standard of care. Also, the introduction of antibodies in the frontline setting will definitely change the game. Thus, even before the use of more sophisticated approaches such as CAR-T cells or T-cell engagers, some TE patients are probably already cured. For NTE patients, similar improvements are already observed, especially with the use of frontline lenalidomide [9]. However, spectacular improvements in PFS in frontline lenalidomide trials should be interpreted with caution, since most of them use continuous lenalidomide, thus prolonging PFS. Whether this longer PFS will automatically translate into longer OS is yet to be demonstrated.

One potential bias in our study is the entry door based on cytogenetic analysis requests. Even though such analyses are currently mandatory for all patients with MM, this was probably not the case in 2005, especially for elderly patients, a fact clearly demonstrated by the significant increase in the number of NTE patients analyzed in the two periods (365–1058). It is plausible that physicians who asked for cytogenetics probably selected the fittest NTE patients in the first period. Thus, survival data for NTE patients in the 2005–2009 period should be interpreted with caution. In contrast, numbers are relatively stable for the TE patients (1567–1821) and are probably less questionable.

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Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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