Multiple myeloma: practice patterns across Europe

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Summary

Real-world data describing management of patients with multiple myeloma are limited. A European (Belgium, France, Germany, Italy, Spain, Switzerland, UK) observational chart review was conducted to address this. Physicians completed questionnaires for every patient seen during a 2–4-week observation period, regardless of treatment status. A total of 435 physicians completed 7635 cross-sectional chart reviews. Overall, 47% of patients were undergoing anti-tumor drug treatment, 42% had previously received ≥1 line of treatment and 12% had never received anti-tumor drug treatment. Of the patients treated by oncologists, onco-hematologists or internists, 95% received, or were expected to receive, at least one line of anti-tumor drug treatment, 61% received ≥2 lines of therapy and 38% received ≥3 lines. Except in the UK, the most commonly used induction therapies contained bortezomib (48%); lenalidomide was the most commonly used first-line maintenance therapy (45%) and second- and third-line agent overall (60% and 52% of patients at those lines, respectively). Bortezomib retreatment was used in 47% of patients who received it first line. Treatment patterns became more diverse with subsequent treatment lines. This study provides insight into real-world treatment patterns in Europe. While treatment practices are broadly similar across countries, some notable differences in the agents used exist.

Keywords multiple myeloma; observational; sequencing, practice patterns; European chart review

Introduction

Multiple myeloma is the second most common hematological malignancy after non-Hodgkin lymphoma, accounting for 13% of blood cancers and 1% of all cancers (Raab, Podar *et al.* 2009). Incidence increases steadily with age; in developed countries, incidence is gradually increasing (Becker 2011) in line with the increasing age of the population.

Over the past three decades, multiple myeloma therapy has changed considerably from the traditional combination of alkylating agents plus steroids, and high-dose chemotherapy and stem cell transplantation (SCT) for younger patients (Kumar, Galeb *et al.* 2011; Torimoto, Shindo *et al.* 2015). Although SCT remains the standard of care for younger patients,[4] almost all patients are now treated with new agents, including the first-in-class proteasome inhibitor bortezomib (Cao, Li *et al.* 2013) and immunomodulatory drugs such as thalidomide, lenalidomide and pomalidomide (Mitsiades and Chen-Kiang 2013). The improved rates and depth of response observed with these new agents, especially when used in triplet combinations, has extended survival and supported the development of new methods of measuring depth of response. The irreversible epoxyketone proteasome inhibitor, carfilzomib (Khan and Badros 2012), and the oral boronic-based proteasome inhibitor, ixazomib (Richardson, Moreau *et al.* 2015), are new and exciting members of a class of agents that is already central to myeloma therapy. In addition, the monoclonal antibodies elotuzumab and daratumumab (Faiman and Richards 2014) represent new mechanisms of action and will therefore complement the current armamentarium. Histone de-acetylase inhibitors (HDACi) are another class of potential anti-myeloma agents, and the pan-HDACi Panobinostat, has recently received marketing authorization in relapsed disease. Thus, the treatment landscape for multiple myeloma is set to change over the next few years. With an ever-increasing choice of agents come many uncertainties, such as the optimal treatment strategy at first and subsequent lines, as well as the best sequence of agents to use in relapsed disease.

Treatment choices are inevitably influenced by approval status and level of drug reimbursement, which vary throughout Europe. Thus, practice patterns also vary, from the management at diagnosis to the number of lines and types of treatment received. Real-world data describing how patients are managed throughout the course of their treatment are limited, however. We conducted an observational, cross-sectional patient chart review to investigate the management of individuals with symptomatic multiple myeloma in Belgium, France, Germany, Italy, Spain, Switzerland and the UK in order to improve the design of future clinical trials and to inform health economic analyses.

Methods

Physicians and patients

The study was performed during 2014. Physicians obtained approval from their respective local ethics committee, if applicable. Ethics committee approval was received in Germany and Spain as per national regulations in these countries.

Physicians completed a questionnaire to ensure that they met study eligibility criteria: having at least 3 years of clinical practice experience, managing at least 10 patients with multiple myeloma per month and having responsibility for treatment initiation.

The chart review comprised cross-sectional and retrospective components, completed concurrently (see Supplementary Material). In the cross-sectional review, physicians completed a questionnaire on patient characteristics and current treatment for all patients seen during the observation period, regardless of the individual's treatment status (i.e. currently receiving active anti-myeloma drug treatment, between lines of therapy, not yet started treatment or receiving palliative care).

The length of the observation period was determined by the physician's monthly caseload: those with large caseloads had 2 weeks to collect data, while those with smaller caseloads had 4 weeks. Patients were included only once during the observation period, even if they were seen multiple times.

In the retrospective review, physicians each completed detailed questionnaires for 12 patients (14 patients in the UK) seen during the previous 3 months and who had completed specific lines of treatment. Patient cases were selected in reverse chronological order. Quotas were defined by line of therapy to ensure sufficient sample size in later lines, for which there is greater patient and treatment heterogeneity (and less consensus among guidelines).

Induction treatment was defined as the first anti-tumor drug treatment received. Progression to the next line was defined as a change of treatment following relapse or toxicity. Retreatment with the same regimen was considered as a new line only if it followed relapse. Maintenance was defined as a new regimen prescribed after the scheduled regimen was completed and the patient had achieved their maximum response, but before disease progression. No formal definition of consolidation was provided. Instead, the anti-tumor drug given after SCT was classified as consolidation.

Physicians were provided with information on staging systems (Durie and Salmon 1975; Greipp, San Miguel *et al.* 2005), European Cooperative Oncology Group (ECOG) performance status, level of response and definitions of treatment stages.

Statistical analyses

Significance was tested using *t*-tests for quantitative variables (significance set at $P<0.05$) and χ^2 tests for categorical variables, with a two-tailed probability threshold of 0.05 considered significant. Results of significance analyses should be interpreted with caution as study was not design to show differences across samples.

The frequency of patient visits is influenced by the anti-tumor drug treatment received and the number of consultations that physicians arrange. These factors affect the probability of patient inclusion. To adjust for this potential bias, patient data collected in the cross-sectional component were weighted by probability of inclusion in the study using the date of the next scheduled consultation (i.e. patients returning sooner were allocated a lower coefficient than those returning later).

The retrospective component was weighted according to the data obtained from the cross-sectional portion using a matching technique (Carpenter and Bithell 2000; van der Laan and Dudoit 2003). The final pooled analysis was adjusted for country contribution size.

Results

Physician and patient characteristics

In total, 435 physicians completed 7635 cross-sectional patient chart reviews and 4997 retrospective patient chart reviews. Most physicians were hematologists (60%) or onco-hematologists (32%), and they were based at university hospitals (44%), non-university centers (29%), specialized cancer centers (14%), offices (8%, all from Germany) and private practices (5%). Notably, no physicians in Switzerland were based at universities. Overall, 79% of the institutes included were part of a hospital network in which at least one center offered SCT, with half (50%) of all institutes having SCT facilities within the hospital.

Patient characteristics for those included in the cross-sectional chart review are described in Table 1. About half (54%) of the patients were male, nearly two-thirds (62%) were at least 65 years old and one-quarter (26%) were older than 75 years. For patients diagnosed in the previous 12 months (i.e. those patients who best represent current clinical diagnostic and treatment procedures), the median age at diagnosis was 68 years (Fig 1). Most (74%) patients had stage II or III disease at diagnosis, according to the international staging system (ISS). Patient characteristics were generally similar across countries.

Of patients undergoing anti-tumor drug treatment at the time of their inclusion in the cross-sectional chart review, 90% were receiving standard anti-tumor drug treatment (i.e. they were not part of a clinical trial or early access program), 7% were enrolled in clinical trials and 3% were enrolled in early access programs.

Stem cell transplantation

In the retrospective analysis, 44% of patients at first line were considered by the physician to be eligible for SCT during their first-line therapy, although only 31% actually received a

transplant (Fig 2). More patients were deemed eligible for SCT in Switzerland (56%), the UK (54%) and Germany (50%) than in the other countries (32–46%; Supplementary Table 1). Despite this difference, the proportion of patients who received SCT (23–35%) was similar in all countries except Switzerland, where all of the patients who were eligible received SCT (56% of patients at first line) (Supplementary Table 1). Patients who received SCT were significantly more likely to be under 65 years old at initiation of first-line therapy than those who did not (79% vs 21%, respectively) and were more likely to have normal renal function (69% vs 53%, respectively) and an ECOG performance status of 0 (25% vs 14%, respectively) at diagnosis (all $p < 0.0001$).

Across all lines, 15% of patients who received SCT also received consolidation therapy (Fig 2). The percentage of patients receiving consolidation therapy ranged from 4% in the UK to 40% in France (data not shown).

As the number of lines of treatment increased, the proportion of patients in the line who had previously received SCT increased. Data showed that 31% of individuals who completed a first-line treatment had received SCT (Fig 2), whereas 70% of patients who completed a fifth or later line of treatment had received SCT at first or second line.

Patients receiving anti-myeloma drug treatment

In the cross-sectional analysis, nearly half (47%) of the 7635 included individuals were currently undergoing anti-tumor drug treatment, with a large proportion receiving first-line therapy (46% of currently treated patients were receiving first-line induction or maintenance; Fig 3). Conversely, 42% patients were not currently receiving anti-tumor drug treatment, but had previously received one or more lines of therapy. Of these previously treated patients, 59% had most recently completed a first-line treatment (Fig 3). The remaining 12% had not yet received any anti-tumor drug treatment.

The main reasons cited for not currently treating individuals were (physicians were permitted to select more than one reason): the patient was in remission and/or had stabilized (61%), the number of planned cycles had been completed (38%), drug holiday (5%), poor overall state of the patient (4%), patient refusal (3% [19% in Germany]) and renal issue (1%). In Switzerland, poor life expectancy was the reason given for 27%.

The reasons cited for patients never receiving treatment were: waiting for more symptoms (62%), waiting for higher blood abnormalities (45%), poor life expectancy (11%) and patient refusal (11%). The mean age of patients not treated because their physicians were waiting for higher blood abnormalities was 67 years, and 80% of these patients were diagnosed with stage I disease (data not shown). The patients who refused treatment tended to be elderly at diagnosis (mean, 76 years), and over half had stage III disease (57%).

Regardless of whether or not patients received SCT, the retrospective data suggested that overall use of maintenance therapy at first line was 12%.

Treatment pathway for patients with symptomatic multiple myeloma

Data from the cross-sectional analysis showed that almost all (95%) patients diagnosed with symptomatic multiple myeloma who were treated by oncologists, onco-hematologists or internists received, or were expected to receive, at least one line of anti-tumor drug treatment (Fig 2). Approximately two-thirds (61%) of individuals received two or more lines of therapy and 38% received three or more lines (Fig 2). In Spain, the proportion of patients receiving later lines of therapy was much lower than in the other countries (e.g. 4% of patients in Spain were receiving third-line treatment compared with 39–60% of those in the other countries; Supplementary Table 2). More patients in Germany (9%) and France (10%) received fifth-line treatment than in the other countries (≤3%; Supplementary Table 2).

Type of treatment received by patients

In the cross-sectional analysis, there was considerable variation in the agents used at each line (Tables 2 and 3). Of patients receiving active treatment at the time of the study, 34% were receiving induction therapy and 12% were receiving first-line maintenance therapy. Overall, in the first-line setting, the most commonly used induction regimens contained bortezomib (48%); in the UK, however, first-line thalidomide-based regimens were used more frequently (56%; Table 2). Lenalidomide was the most commonly used first-line maintenance therapy (45%; Table 2) and was also the most commonly used second- and third-line agent in most countries (60% and 52% of patients overall in second- and third-line, respectively; Table 3), although in the UK bortezomib-containing regimens were the most commonly used second-line regimens (62%).

While, at the time of the study, pomalidomide was not universally reimbursed in either Italy or the UK, and had only recently received reimbursement in the other countries studied, its use was prominent in fourth and later lines (34%). Bendamustine was seldom used in first- or second-line therapy (2% and 3%, respectively), but was more commonly used in third line in Germany, Spain and France (Table 3).

Treatment sequencing pathway

As noted above, bortezomib was the most common treatment used first-line. In the retrospective analysis, of 750 patients who received bortezomib at first line, 26% received it again at second line, and 20% of those patients received it again at third line (Fig 4a). A large proportion (61%) of patients who received bortezomib at first line went on to receive lenalidomide at second line; for these patients, the most frequent third-line therapy was bendamustine (40%), although 25% received retreatment with bortezomib and 14% received pomalidomide. The majority of patients (59%) who had previously received second-line bortezomib went on to receive third-line lenalidomide. Overall, bortezomib retreatment was used in 43% of patients who received the agent at first line.

Of patients who received first-line thalidomide (excluding those who received thalidomide in combination with bortezomib), 76% received bortezomib in the second-line setting and 17% received lenalidomide-based regimens (Fig 4b). Most (69%) of those who received second-line lenalidomide went on to receive bortezomib, although pomalidomide, bendamustine, and thalidomide were also used in the third line (Fig 4b). Of those patients who received second-line bortezomib following first-line thalidomide, the majority (80%) subsequently received third-line lenalidomide. Overall, of the patients who initially received bortezomib or thalidomide and who subsequently received third-line treatment, 30% had been retreated with bortezomib.

Overall, treatment sequencing pathways were similar regardless of whether patients had received SCT.

Discussion

This study summarizes cross-sectional data on over 7000 patients with symptomatic multiple myeloma being managed in 2014 across seven European countries. The physicians completing the chart audit were haematologists or haemato-oncologists treating a large number of patients and who are based in centres with large haematology practices, as reflected by the access to SCT facilities. Thus, these data can be considered to be representative of current real-world treatment patterns in Europe.

Information on real-world practice in the selection of therapies for newly-diagnosed and relapsed patients will aid investigators in designing clinical trials and selecting appropriate comparators. These data will also be important for pharmaceutical companies engaged in research to develop appropriate therapies for the treatment and management of multiple myeloma and was one of the factors driving this important study. Establishing how or, indeed, whether the findings of previous clinical trials have been implemented in real life can inform the design of future clinical studies. Understanding how physicians use an agent, on- or off-licence, can often give insights into how new agents can be incorporated into treatment pathways to maximize patient benefit. Finally, such data can be used to inform health economic analyses which are frequently required by reimbursement authorities.

The results show that first- and second-line treatment practices are generally similar across Europe, with bortezomib used most commonly in the first line and lenalidomide used most commonly at second-line. Indeed, these patterns reflect the recommendations given in European guidelines for multiple myeloma (Moreau, San Miguel *et al.* 2013; Ludwig, Sonneveld *et al.* 2014). The UK was the only exception to this general pattern, where use of thalidomide first line pushes bortezomib to second-line therapy and lenalidomide to third-line therapy, reflecting guidance from the UK National Institute for Health and Care Excellence (NICE) at the time of the study (National Institute for Health and Care Excellence 2011). More recently, however, NICE has updated its guidance to recommend first-line bortezomib

for the induction treatment of adults with previously untreated multiple myeloma, who are eligible for high-dose chemotherapy with hematopoietic stem cell transplantation (National Institute for Health and Care Excellence 2014). Treatment practices in the UK may therefore change.

The best sequence of available treatment options for patients with newly diagnosed multiple myeloma has not been established, and there are no standard practices or globally adopted treatment guidelines. Both The International Myeloma Working Group (IMWG) recommendations and the US National Comprehensive Cancer Network (NCCN) treatment guidelines list several preferred regimens and a number of alternative regimens as options for primary, maintenance and salvage therapy for patients with multiple myeloma, but they do not recommend any one approach over another (Ludwig, Miguel *et al.* 2014; National Comprehensive Cancer Network 2015). Furthermore, there is no standard of care or optimal choice for individuals with relapsed or refractory multiple myeloma. Choice of treatment depends on a range of factors, including the type of and response to previous therapies, tumor characteristics and patient health and comorbidities. This lack of consensus is reflected in the results of the present study, in which the regimens prescribed, particularly for third line and beyond, were diverse, even within the same country.

Treatment pathways reflect a need to sequence different mechanisms of action or to re-treat with similar regimen based on prior response and treatment free intervals. At the time of the chart review, treatment options were limited for patients with multiple myeloma refractory to bortezomib and lenalidomide therapy. The cross-sectional analysis found that individuals who received first-line bortezomib were often retreated with bortezomib at later lines. While bortezomib retreatment can produce good clinical outcomes (Knopf, Duh *et al.* 2014), the use of alternative agents in later lines (e.g. pomalidomide and bendamustine) can also be effective and may avoid accumulation of toxicity (San Miguel, Weisel *et al.* 2013; Lau, Smith *et al.* 2015). Furthermore, new agents such as carfilzomib, ixazomib, panobinostat, elotuzumab and daratumumab are now becoming options for those whose disease

progressed in previous lines of therapies, helping to avoid the need for re-treatment with the same agent in multiple lines.

High-dose therapy followed by autologous SCT is considered the standard of care for those younger than 65 years of age without significant comorbidity, offering the chance of a prolonged disease- and treatment-free period (Ludwig, Avet-Loiseau *et al.* 2012; Ludwig, Miguel *et al.* 2014). In the present study, approximately one-third of patients at the end of induction therapy had received SCT; this proportion was similar across the countries studied. Furthermore, results from this study showed that the percentage of patients who had received SCT increased with each line of treatment, indicating that individuals who had a successful SCT were more likely to receive further lines of therapy. With respect to patient baseline characteristics, this finding suggests that physicians were following guideline recommendations to treat patients younger than 65 years with SCT (Moreau, San Miguel *et al.* 2013).

Several factors may underlie a physician's decision to initiate therapy and the choice of agent(s) to use; these include patient performance status, response to previous therapy, lack of evidence for treatment options in later lines and country-specific reimbursement policies or local guidelines influencing treatment decisions in later lines. In the current study, the percentage of patients being treated at each subsequent treatment line decreased sharply, reflecting the increasing number of individuals who did not receive further lines of therapy after each relapse, or who died before reaching the next line of therapy. This is perhaps surprising given the activity of bortezomib and lenalidomide in second- and third-line settings (Richardson, Sonneveld *et al.* 2005; Dimopoulos, Spencer *et al.* 2007; Richardson, Sonneveld *et al.* 2007; Weber, Chen *et al.* 2007) and the availability of bendamustine and pomalidomide for patients refractory to these agents. Again, this finding could reflect limited access to new agents in real-world practice. It is also possible that patients undergoing later lines of treatment are managed in other healthcare settings, such as primary or palliative care, and so would not have been included in this study. In particular, a large proportion of

patients in Spain discontinued treatment between the second and third lines, and so very few records were collected for patients receiving treatment in the third-line setting and beyond.

One interesting finding from the present study was that the cross-sectional patient records collected included only a small proportion of those taking part in a clinical trial at the time of their inclusion in this observational study. This is unexpected given the recommendations in clinical guidelines that patients with relapsed and refractory disease should be offered participation in trials when possible (Moreau, San Miguel *et al.* 2013; National Comprehensive Cancer Network 2015), but is indicative of the real-life practice in each of the countries.

While the results of this study provide an important overview of treatment practices across Europe, there are some considerations that should be borne in mind when interpreting the results. For example, bortezomib is generally given for a fixed duration whereas the label for lenalidomide is continuous therapy. This may have resulted in a reduced representation of patients receiving bortezomib. Individuals not undergoing anti-tumor drug treatment may also have been under-represented, because such patients may be managed in the interim by different physicians not included in the study. In addition, it should be noted that the study was conducted 3–7 months earlier in France, Italy, and the UK than in the other countries; as the use of pomalidomide was increasing over the time period of the study, this may have affected results recorded in these countries relative to Belgium, Germany, Spain, Switzerland and the UK.

In summary, we present the results of a cross-sectional study on treatment practices in over 7000 patients with multiple myeloma across several European countries. The notable findings are that while there is consistency in agents used at first and second line, the treatments utilized at later treatment lines are more varied. In addition, re-treatment with bortezomib is common practice in nearly half of patients arriving at second and third line

therapy. A surprisingly low proportion of patients appear to be treated on clinical trials, indicating an area for improvement in clinical practice. These real-world data provide useful information for both designing clinical trials and health economic evaluations of new and existing agents.

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References

Becker, N. (2011). Epidemiology of multiple myeloma. *Recent Results in Cancer Research* **183**: 25–35.

Cao, B., J. Li and X. Mao (2013). Dissecting bortezomib: development, application, adverse effects and future direction. *Current Pharmaceutical Design* **19**: 3190–3200.

Carpenter, J. and J. Bithell (2000). Bootstrap confidence intervals: when, which, what? A practical guide for medical statisticians. *Statistics in Medicine* **19**: 1141–1164.

Dimopoulos, M., A. Spencer, M. Attal, H. M. Prince, J. L. Harousseau, A. Dmoszynska, J. San Miguel, A. Hellmann, T. Facon, R. Foa, A. Corso, Z. Masliak, M. Olesnyckyj, Z. Yu, J. Patin, J. B. Zeldis and R. D. Knight (2007). Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. *New England Journal of Medicine* **357**: 2123–2132.

Durie, B. G. and S. E. Salmon (1975). A clinical staging system for multiple myeloma. Correlation of measured myeloma cell mass with presenting clinical features, response to treatment, and survival. *Cancer* **36**: 842–854.

Faiman, B. and T. Richards (2014). Innovative agents in multiple myeloma. *J Adv Pract Oncol* **5**: 193–202.

Greipp, P. R., J. San Miguel, B. G. Durie, J. J. Crowley, B. Barlogie, J. Blade, M. Boccadoro, J. A. Child, H. Avet-Loiseau, R. A. Kyle, J. J. Lahuerta, H. Ludwig, G. Morgan, R. Powles, K. Shimizu, C. Shustik, P. Sonneveld, P. Tosi, I. Turesson and J. Westin (2005). International staging system for multiple myeloma. *Journal of Clinical Oncology* **23**: 3412–3420.

Khan, R. Z. and A. Badros (2012). Role of carfilzomib in the treatment of multiple myeloma. *Expert Rev Hematol* **5**: 361–372.

Knopf, K. B., M. S. Duh, M. H. Lafeuille, J. Gravel, P. Lefebvre, L. Niculescu, A. Ba-Mancini, E. Ma, H. Shi and R. L. Comenzo (2014). Meta-analysis of the efficacy and safety of bortezomib re-treatment in patients with multiple myeloma. *Clin Lymphoma Myeloma Leuk* **14**: 380-388.

Kumar, A., S. Galeb and B. Djulbegovic (2011). Treatment of patients with multiple myeloma: an overview of systematic reviews. *Acta Haematologica* **125**: 8–22.

Lau, I. J., D. Smith, R. Aitchison, N. Blesing, P. Roberts, A. Peniket, K. Yong, N. Rabin and K. Ramasamy (2015). Bendamustine in combination with thalidomide and dexamethasone is a viable salvage option in myeloma relapsed and/or refractory to bortezomib and lenalidomide. *Annals of Hematology* **94**: 643–649.

Ludwig, H., H. Avet-Loiseau, J. Blade, M. Boccadoro, J. Cavenagh, M. Cavo, F. Davies, J. de la Rubia, S. Delimpasi, M. Dimopoulos, J. Drach, H. Einsele, T. Facon, H. Goldschmidt, U. Hess, U. H. Mellqvist, P. Moreau, J. San-Miguel, P. Sondergeld, P. Sonneveld, M. Udvardy and A. Palumbo (2012). European perspective on multiple myeloma treatment strategies: update following recent congresses. *The Oncologist* **17**: 592-606.

Ludwig, H., J. S. Miguel, M. A. Dimopoulos, A. Palumbo, R. Garcia Sanz, R. Powles, S. Lentzsch, W. Ming Chen, J. Hou, A. Jurczyszyn, K. Romeril, R. Hajek, E. Terpos, K. Shimizu, D. Joshua, V. Hungria, A. Rodriguez Morales, D. Ben-Yehuda, P. Sondergeld, E. Zamagni and B. Durie (2014). International Myeloma Working Group recommendations for global myeloma care. *Leukemia* **28**: 981–992.

Ludwig, H., P. Sonneveld, F. Davies, J. Blade, M. Boccadoro, M. Cavo, G. Morgan, J. de la Rubia, M. Delforge, M. Dimopoulos, H. Einsele, T. Facon, H. Goldschmidt, P. Moreau, H. Nahi, T. Plesner, J. San-Miguel, R. Hajek, P. Sondergeld and A. Palumbo (2014). European perspective on multiple myeloma treatment strategies in 2014. *The Oncologist* **19**: 829–844.

Mitsiades, C. S. and S. Chen-Kiang (2013). Immunomodulation as a therapeutic strategy in the treatment of multiple myeloma. *Critical Reviews in Oncology/Hematology* **88 Suppl 1**: S5–13.

Moreau, P., J. San Miguel, H. Ludwig, H. Schouten, M. Mohty, M. Dimopoulos and M. Dreyling (2013). Multiple myeloma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology* **24 Suppl 6**: vi133–137.

National Comprehensive Cancer Network. (2015). Clinical practice guidelines in oncology. Multiple myeloma. Version 4, 2015. Retrieved May, 2015, from http://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf.

National Institute for Health and Care Excellence. (2011). Bortezomib and thalidomide for the first‐line treatment of multiple myeloma. Retrieved July, 2015, from http://www.nice.org.uk/guidance/ta228.

National Institute for Health and Care Excellence. (2014). Bortezomib for induction therapy in multiple myeloma before high-dose chemotherapy and autologous stem cell transplantation. Retrieved July, 2015, from http://www.nice.org.uk/guidance/ta311.

Raab, M. S., K. Podar, I. Breitkreutz, P. G. Richardson and K. C. Anderson (2009). Multiple myeloma. *Lancet* **374**: 324–339.

Richardson, P. G., P. Moreau, J. P. Laubach, N. Gupta, A. M. Hui, K. C. Anderson, J. F. San Miguel and S. Kumar (2015). The investigational proteasome inhibitor ixazomib for the treatment of multiple myeloma. *Future Oncol* **11**: 1153–1168.

Richardson, P. G., P. Sonneveld, M. Schuster, D. Irwin, E. Stadtmauer, T. Facon, J. L. Harousseau, D. Ben-Yehuda, S. Lonial, H. Goldschmidt, D. Reece, J. S. Miguel, J. Blade, M. Boccadoro, J. Cavenagh, M. Alsina, S. V. Rajkumar, M. Lacy, A. Jakubowiak, W. Dalton, A. Boral, D. L. Esseltine, D. Schenkein and K. C. Anderson (2007). Extended follow-up of a phase 3 trial in relapsed multiple myeloma: final time-to-event results of the APEX trial. *Blood* **110**: 3557–3560.

Richardson, P. G., P. Sonneveld, M. W. Schuster, D. Irwin, E. A. Stadtmauer, T. Facon, J. L. Harousseau, D. Ben-Yehuda, S. Lonial, H. Goldschmidt, D. Reece, J. F. San-Miguel, J. Blade, M. Boccadoro, J. Cavenagh, W. S. Dalton, A. L. Boral, D. L. Esseltine, J. B. Porter, D. Schenkein and K. C. Anderson (2005). Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. *New England Journal of Medicine* **352**: 2487–2498.

San Miguel, J., K. Weisel, P. Moreau, M. Lacy, K. Song, M. Delforge, L. Karlin, H. Goldschmidt, A. Banos, A. Oriol, A. Alegre, C. Chen, M. Cavo, L. Garderet, V. Ivanova, J. Martinez-Lopez, A. Belch, A. Palumbo, S. Schey, P. Sonneveld, X. Yu, L. Sternas, C. Jacques, M. Zaki and M. Dimopoulos (2013). Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, phase 3 trial. *Lancet Oncol* **14**: 1055–1066.

Torimoto, Y., M. Shindo, K. Ikuta and Y. Kohgo (2015). Current therapeutic strategies for multiple myeloma. *Int J Clin Oncol* **20**: 423–430.

van der Laan, M. J. and S. Dudoit. (2003). Unified cross-validation methodology for selection among estimators and a general cross-validated adaptive epsilon-net estimator: finite sample oracle inequalities and examples. U.C. Berkeley Division of Biostatistics Working Paper Series. Working Paper 130. Retrieved July, 2015, from http://biostats.bepress.com/ucbbiostat/paper130.

Weber, D. M., C. Chen, R. Niesvizky, M. Wang, A. Belch, E. A. Stadtmauer, D. Siegel, I. Borrello, S. V. Rajkumar, A. A. Chanan-Khan, S. Lonial, Z. Yu, J. Patin, M. Olesnyckyj, J. B. Zeldis and R. D. Knight (2007). Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. *New England Journal of Medicine* **357**: 2133–2142.

Table 1. Characteristics of patients included in the cross-sectional chart review.

	All (n=7635)	Belgium (n=192)	France (n=1770)	Germany (n=1817)	Italy (n=1710)	Spain (n=1007)	Switzerland (n=115)	UK (n=1024)
Sex (%)								
Male	54	52	52	52	53	58	57	64
Female	46	48	48	48	47	42	43	36
Age at time of inclusion in the study (%)								
<65 years	38	28	37	39	38	43	22	38
65–75 years	36	25	33	39	35	39	44	41
>75 years	26	46	30	22	27	19	33	21
Body surface area (m^2)								
Median	1.75	1.74	1.80	1.80	1.70	1.70	1.80	1.80
Range	1.17–2.60	1.23–2.38	1.34–2.60	1.30–2-13	1.20–2.30	1.20–2.40	1.17–2.52	1.50–2.22
ISS score at diagnosis (%)								
I	23	26	19	24	23	26	23	24
II	37	16	29	29	44	51	42	43
III	37	46	49	35	30	24	34	33
Unknown	4	12	3	12	3	0	1	0
Median time since diagnosis (months)	33	26	40	26	29	36	26	33

Owing to rounding, percentages may not sum to 100%. Patient numbers for all countries may differ from the total of the individual countries owing to weighting of the data.

ISS, International Staging System.

Table 2. First-line treatments received by patients at the time of the study.

	ALL	Belgium	France	Germany	Italy	Spain	Switzerland	UK
All first-line treatments	**n=1612**	**n=53**	**n=338**	**n=290**	**n=415**	**n=359**	**n=26**	**n=178**
Bortezomib	36	26	37	**48**	**28**	**49**	43	**22**
Lenalidomide	15	**4**	**10**	**21**	18	14	25	17
Bortezomib + lenalidomide	1	2	**3**	1	0	1	0	0
Bortezomib + thalidomide	11	**26**	**15**	**0**	**21**	**8**	13	**1**
Thalidomide	21	31	25	**7**	17	0	6	**55**
Bendamustine	2	0	1	**7**	0	1	7	0
Pomalidomide	<1	0	0	<1	0	0	0	<1
Melphalan + prednisone	7	12	5	5	7	**19**	2	**3**
Other	7	**0**	**4**	**11**	9	9	5	**3**
Induction	**n=1196**	**n=37**	**n=264**	**n=206**	**n=253**	**n=298**	**n=14**	**n=153**
Bortezomib	43	35	38	**63**	39	**55**	50	**24**
Lenalidomide	5	3	4	6	5	3	0	**11**
Bortezomib + lenalidomide	1	0	**4**	1	0	1	0	0
Bortezomib + thalidomide	14	**28**	18	**0**	**34**	**8**	23	**1**
Thalidomide	20	19	24	**6**	**9**	**0**	6	**59**
Bendamustine	2	0	2	**9**	0	2	**13**	0
Pomalidomide	<1	0	0	0	0	0	0	<1
Melphalan + prednisone	9	15	6	6	10	**22**	0	**3**
Other	6	0	4	10	5	9	8	**2**
Maintenance	**n=416**	**n=16**	**n=74**	**n=84**	**n=162**	**n=61**	**n=12**	**n=25**
Bortezomib	17	6	**34**	13	11	17	35	7
Lenalidomide	44	**5**	**31**	**60**	38	**70**	55	51
Bortezomib + lenalidomide	1	4	0	1	1	0	0	0
Bortezomib + thalidomide	3	**21**	4	0	1	5	0	0
Thalidomide	24	**58**	28	**11**	30	0	5	35
Bendamustine	1	0	1	0	1	0	0	0
Pomalidomide	<1	0	0	1	0	0	0	0
Melphalan + prednisone	1	5	0	1	2	0	5	0
Other	10	0	2	15	16	8	0	7

Data from the cross-sectional analysis. Data show the percentages of patients receiving each type of therapy; values in bold differ significantly from the mean for all countries (P<0.05). Owing to rounding, percentages may not sum to 100%. Patient numbers for all countries may differ from the total of the individual countries owing to weighting of the data.

Table 3. Second-, third- and subsequent-line treatments received by patients at those lines at the time of the study.

	ALL	Belgium	France	Germany	Italy	Spain	Switzerland	UK
Second line	**n=934**	**n=35**	**n=258**	**n=198**	**n=198**	**n=133**	**n=7**	**n=107**
Bortezomib	23	**8**	**11**	18	25	17	6	**59**
Lenalidomide	59	**84**	**77**	61	60	54	67	**19**
Bortezomib + lenalidomide	1	0	2	0	1	0	0	3
Bortezomib + thalidomide	1	0	1	0	1	**6**	0	0
Thalidomide	7	0	4	7	**3**	**16**	12	12
Bendamustine	3	2	3	**6**	2	2	0	1
Pomalidomide	0	0	1	1	0	0	0	0
Melphalan + prednisone	2	0	1	4	3	1	**16**	0
Other	4	6	2	4	7	4	0	5
Third line	**n=641**	**n=19**	**n=169**	**n=130**	**n=161**	**n=48**	**n=6**	**n=95**
Bortezomib	12	9	9	14	15	20	35	7
Lenalidomide	51	63	43	**32**	52	**18**	42	**87**
Bortezomib + lenalidomide	1	0	0	1	1	2	0	0
Bortezomib + thalidomide	0	0	0	0	0	0	0	0
Thalidomide	4	0	7	2	5	0	0	1
Bendamustine	14	7	19	**25**	**7**	24	0	**3**
Pomalidomide	12	7	21	15	9	16	23	**1**
Melphalan + prednisone	2	**10**	0	2	3	**10**	0	0
Other	5	5	2	9	8	11	0	2
Subsequent lines	**n=370**	**n=9**	**n=126**	**n=106**	**n=70**	**n=3**	**n=5**	**N=39**
Bortezomib	10	8	8	13	14	29	25	2
Lenalidomide	24	51	19	25	22	0	33	34
Bortezomib + lenalidomide	0	0	0	1	0	**29**	0	0
Bortezomib + thalidomide	1	0	2	0	0	**21**	0	2
Thalidomide	6	0	**1**	8	6	7	0	**19**
Bendamustine	11	0	13	13	11	0	11	7
Pomalidomide	34	5	**49**	33	**15**	0	27	32
Melphalan + prednisone	2	9	0	1	**7**	0	0	2
Other	11	28	8	7	**26**	14	4	3

Data from the cross-sectional analysis. Data show the percentages of patients receiving each type of therapy; values in bold differ significantly from the mean for all countries (P<0.05). Owing to rounding, percentages may not sum to 100%.

Figure legends

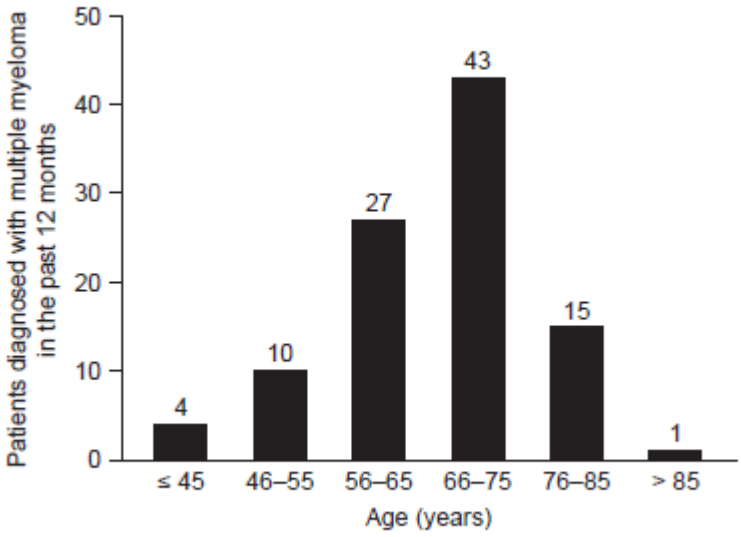
Fig 1. Age at diagnosis of patients with multiple myeloma diagnosed in the previous12 months.

Fig 2. Treatment pathway for patients with symptomatic multiple myeloma.

Fig 3. Treatment status of patients with symptomatic multiple myeloma.

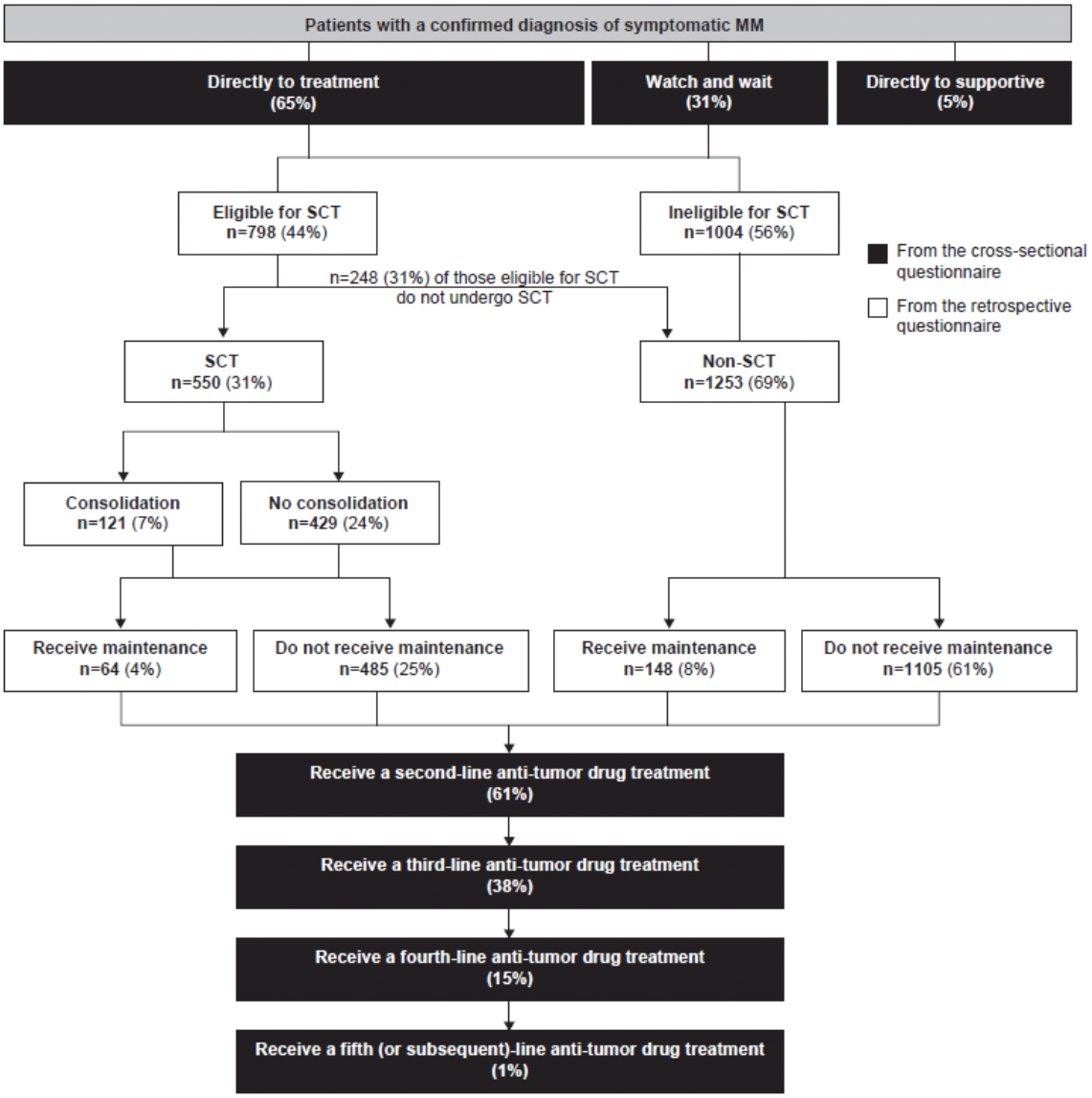
Fig 4. Sequence of treatment for patients receiving (a) first-line bortezomib-based regimens and (b) first-line thalidomide-based regimens.

Fig 1. Age at diagnosis of patients with multiple myeloma diagnosed in the previous12 months.



Data from the cross-sectional analysis.

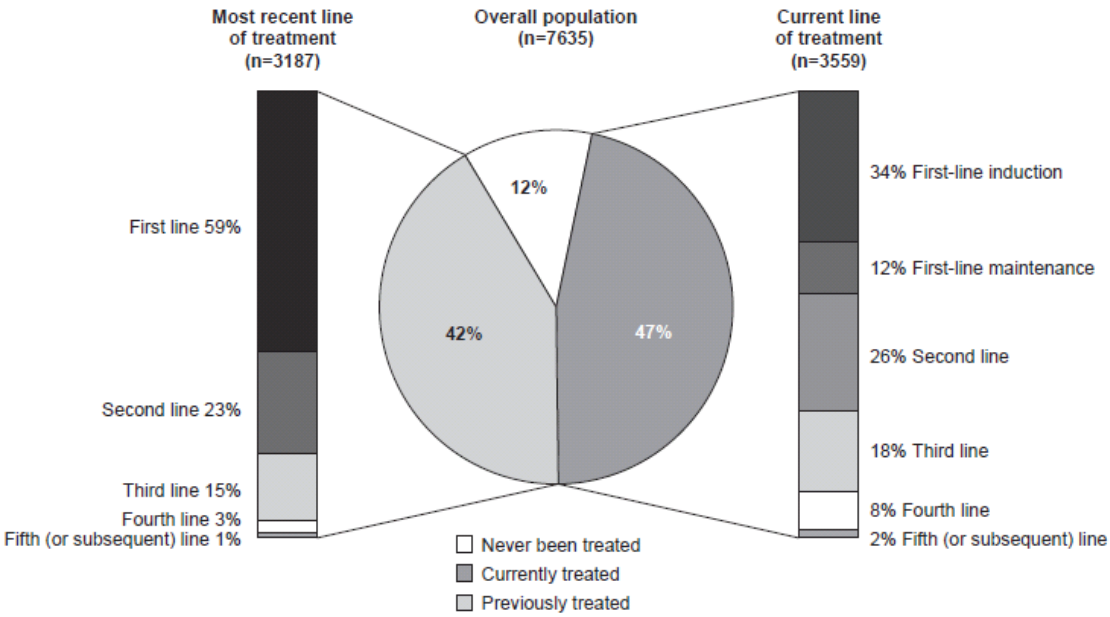
Fig 2. Treatment pathway for patients with symptomatic multiple myeloma.



Cross-sectional data are based on all case report forms completed (n=7635); retrospective data are based on case report forms for patients who completed a first-line therapy (n=1802). Total patient numbers vary slightly across the chart owing to weighting. Owing to rounding, percentages may not add to 100%.

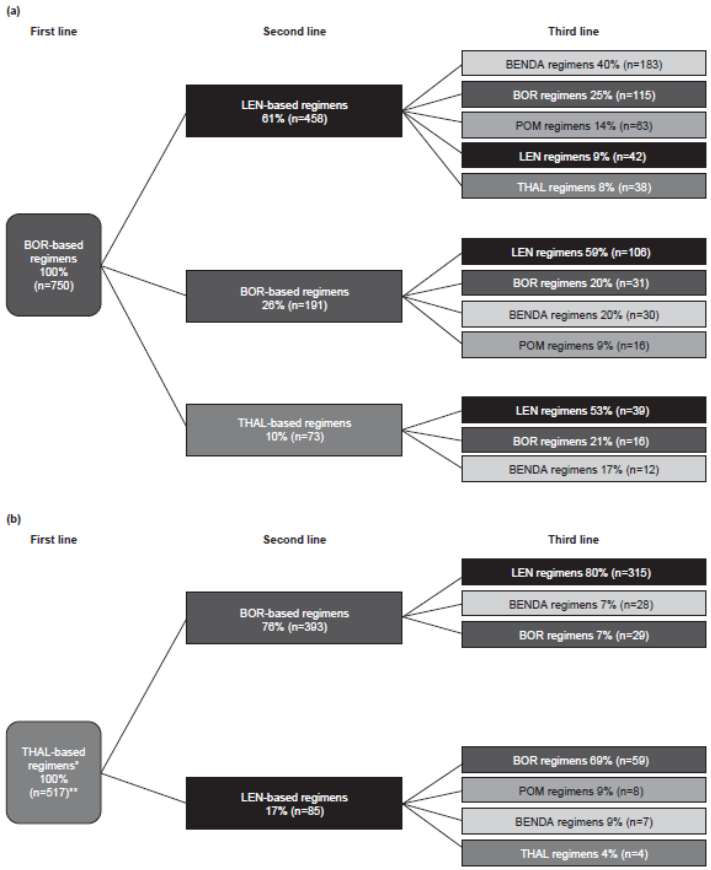
SCT, stem cell transplantation.

Fig 3. Treatment status of patients with symptomatic multiple myeloma.



Data from the cross-sectional analysis. Owing to rounding, percentages may not sum to 100%.

Fig 4. Sequence of treatment for patients receiving (a) first-line bortezomib-based regimens and (b) first-line thalidomide-based regimens.



Data are from the retrospective analysis and show the proportion of patients receiving first-line bortezomib-based treatment who went on to receive each subsequent line of treatment. Percentages indicate the proportion of patients from the previous line who received the subsequent line of treatment. Owing to rounding, percentages may not sum to 100%. BENDA, bendamustine; BOR, bortezomib; LEN, lenalidomide; POM,

pomalidomide; THAL, thalidomide. *Excludes regimens containing both bortezomib and thalidomide; **UK, n=275; France, n=91; Italy, n=65; Germany, n=51; Belgium, n=16; Switzerland, n=12; Spain, n=7.