Observational study of multiple myeloma in Latin America

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Abstract Relatively little is known about the outcomes of multiple myeloma in Latin America, a world region where incorporation of novel agents is generally slow. In the current retrospective-prospective study, we aimed to describe the patterns of care and treatment results in five Latin American countries. Between April 2007 and October 2009, patients who had been diagnosed from January 2005 to December 2007 were registered at 23 institutions from Argentina, Brazil, Chile, Mexico, and Peru. We divided patients into two cohorts, according to transplantation eligibility, and analyzed them with regard to first-line treatment and overall survival (OS). We analyzed a total of 852 patients, 46.9 % of whom were female. The median follow-up was 62 months.

Among transplantation-ineligible patients ($N = 461$), the mean age was 67.4 years, approximately one third of patients received a thalidomide-based treatment in the first line, and the median OS was 43.0 months. Transplantation-eligible patients ($N = 391$) had a mean age of 54.7 years and a median OS of 73.6 months. Autologous transplantation was performed in 58.6 % of the patients for whom this procedure was initially planned and in only 26.9 % of the overall patients. Our long-term results reflect the contemporary literature for patients with multiple myeloma treated with autologous transplantation and thalidomide-based regimens in clinical trials and observational studies. However, further efforts are needed to approve and incorporate novel agents in Latin American

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countries, as well as to increase access to transplantation, in order to achieve the expected improvements in patient outcomes.

Keywords Multiple myeloma · Survival analysis · Thalidomide · Transplantation · Autologous

Introduction

Multiple myeloma is thought to account for nearly 1 % of all cancers and 15 % of hematologic malignancies [1, 2]. However, its incidence varies in different countries and ethnic groups. It is well known, for example, that the incidence of multiple myeloma is higher in blacks than in whites [3]. Conversely, the incidence of multiple myeloma is lower in Asia than in the USA and Western Europe; nevertheless, a progressive increase in the incidence of multiple myeloma has been reported in some Asian countries [4]. The clinical features of multiple myeloma may also differ across world regions, and it is important to characterize the profile of this disease in different geographic locations [5]. Finally, patient outcomes may also vary across countries and world regions as a result of differing biological features, stage at presentation, and availability of novel therapies.

Relatively little is known about the incidence, clinical features, and outcomes of multiple myeloma in Latin America, a world region where relatively free miscegenation of populations of Native American, Mediterranean, and African ancestry has occurred for several centuries. In Latin America, novel therapies tend to be approved at later stages than in the USA or European countries. As a result, access to agents such as bortezomib and lenalidomide is usually limited under the current public health systems of many Latin American countries. On the other hand, thalidomide has been available for patients with multiple myeloma and at a low cost in many of these countries for several years. In a previous study, we retrospectively assessed 1112 patients with multiple myeloma diagnosed in Brazil between 1998 and 2004, and our results suggested that the majority of the patients in this country present with advanced disease upon diagnosis [6]. Moreover, that study confirmed the prognostic utility of the International Staging System (ISS) [7] among these patients. Finally, the study demonstrated that the registration of patients with multiple myeloma is feasible in Brazilian institutions that are highly motivated. This led us to design the current observational study, with the main goals of gaining further insight about multiple myeloma by including other Latin American countries, describing the patterns of care and treatment results in this world region, and allowing participating investigators to share information on the demographic and clinical features of their patients.

Methods

Study design and oversight

This was an international, multicenter, retrospective-prospective study conducted under the auspices of the Latin American International Myeloma Foundation. The protocol for the study was approved by the institutional review board of all participating institutions, and written informed consent was obtained from all patients. Treatment and patient evaluation were left to the discretion of the participating investigators and local standards of care. The initial goal was to enroll approximately 1500 patients from nearly 30 centers from seven Latin American countries (Argentina, Brazil, Chile, Colombia, Mexico, Peru, and Venezuela). Patient registration was done between April 2007 and October 2009, and eligible patients were those diagnosed between 1 January 2005 and 31 December 2007. Therefore, for the majority of patients, registration was done in a retrospective fashion, whereas follow-up was prospective until the time of the database lock, on 31 December 2012. A follow-up period of at least 5 years for each patient was foreseen, unless death or loss to follow-up ensued before.

Selection criteria and collected data

Participating institutions were selected on the basis of clinical expertise and expected accrual. The chief inclusion criterion was the presence of multiple myeloma according to the International Myeloma Working Group criteria [8], and patients with any plasma cell- or immunoglobulin-related disorders other than multiple myeloma were excluded. None of the patients enrolled in the current study participated in our previous study [6]. Demographic and clinical data were gathered from institutional charts by locally designated individuals and were entered into a central, web-based registry specifically designed for the study. Such data included the date of diagnosis, the stage according to the Durie-Salmon staging (DSS) system [9] and the ISS [7], the type of monoclonal component, the results of relevant baseline laboratory tests, the eligibility for autologous transplantation, the types and dates of treatments administered, and the date of the last follow-up or death. No data on toxicity or quality of life were collected for the study. Data monitoring and analysis were performed by a contract research organization under the supervision of study investigators and sponsors, and the authors vouch for the full contents of the manuscript, which was drafted and reviewed without any involvement with commercial sponsors.

Statistical analysis

For the statistical analysis, two populations were defined on the basis of eligibility for transplantation. Transplantation-ineligible patients were analyzed as such (none of the patients

who were initially ineligible underwent transplantation). On the other hand, not all the transplantation-eligible patients underwent transplantation for various reasons that were not investigated; however, these patients were analyzed in the transplantation-eligible group, along with those undergoing transplantation.

Overall survival (OS), the primary outcome measure, was defined as the time elapsed between the first day of the first treatment administered to each patient and death from any cause, with censoring of patients who were alive in the last follow-up. OS was estimated by the Kaplan-Meier method, and differences between groups were compared using the log-rank test. For the analysis of OS according to receipt of transplantation, the landmark method was used [10]. The median follow-up was estimated using the reverse Kaplan-Meier method [11]. Two-sided p values <0.05 were considered statistically significant. Statistical analysis was performed using MedCalc®, version 11.0.0.0 (Mariakerke, Belgium).

Results

Overview of patient accrual and follow-up

A total of 852 patients diagnosed between January 2005 and December 2007 were registered between April 2007 and October 2009 at 23 institutions from Argentina, Brazil, Chile, Mexico, and Peru. The median follow-up on survival for the 852 patients was 62 months.

Transplantation-ineligible patients

Of the 852 patients, 461 (54.1 %) were ineligible for autologous transplantation. Table 1 presents their main demographic and clinical features, as well as their country of enrollment. The mean age was 67.4 years, nearly two thirds of the patients had DSS stage III disease, and 37.9 % had ISS stage III disease. Nearly one third of the patients received a thalidomide-based treatment in the first line, and subsequent lines of therapies were administered to nearly half of the patients in the second line and 15 % in the third line. None of the patients received either bortezomib or lenalidomide in the first line. The available data allowed for the analysis of OS in 441 of 461 transplantation-ineligible patients. Their survival experience is depicted in Fig. 1. Their median OS was 43.0 months, with an estimated survival rate of approximately 38 % at 5 years. With regard to the use of thalidomide in the first-line regimen, there was no significant difference in the OS according to this use (medians of 42.8 and 44.1 months for patients with and without thalidomide, respectively; hazard ratio, 0.91; 95 % confidence interval, 0.68–1.21; $p = 0.508$).

Transplantation-eligible patients

Of the 852 patients, 391 (45.9 %) were initially eligible for autologous transplantation upon diagnosis. Table 1 presents their main features. Their mean age was 54.7 years, nearly 72 % of the patients had DSS stage III disease, and 30 % had ISS stage III disease. Transplantation-ineligible patients were on average nearly 13 years older, more likely to be female, and more likely to present with ISS stage III disease than transplantation-eligible patients. The most common first-line regimens were vincristine/doxorubicin/dexamethasone or an equivalent regimen, which were administered to nearly two thirds of patients; thalidomide/dexamethasone was used in approximately 20 % of the patients, with all other regimens comprising only 16.9 % of the cases (none of the patients received either bortezomib or lenalidomide in the first line). Autologous transplantation was actually administered to only 58.6 % of patients for whom this procedure was planned and in 26.9 % of the 852 overall patients. Subsequent lines of therapies were administered to 64.2 % of the transplantation-eligible patients in the second line and 25.3 % in the third line. Of note is that bortezomib and/or lenalidomide were given to less than 10 % of these patients as rescue therapy. Once again, there was no significant difference in the OS according to the use of thalidomide in the first-line regimen (medians of 60.5 and 79.5 months for patients with and without the agent, respectively; hazard ratio, 1.12; 95 % confidence interval, 0.75–1.68; $p = 0.570$).

The available data allowed for the analysis of OS in 388 of 391 transplantation-eligible patients. Their survival experience is depicted in Fig. 2. Patient median OS was 73.6 months, with an estimated survival rate of approximately 56 % at 5 years. Considering patients who underwent transplantation, the procedure was done after a median of 9.4 months (interquartile range, 6.8–13.8 months) after treatment initiation. Among transplantation-eligible patients who were alive at 12 months ($N = 320$), a landmark analysis was performed comparing the OS of those who indeed underwent the procedure before the landmark ($N = 133$) and those who, despite an initial recommendation, did not undergo transplantation or had it after the landmark of 12 months ($N = 187$). The OS from the landmark did not differ significantly between patients who did and who did not undergo transplantation (median OS not reached in both groups; hazard ratio, 0.85; 95 % confidence interval, 0.59–1.23; $p = 0.398$).

Baseline prognostic factors overall

For the overall patient sample, we assessed conventional prognostic factors for OS. There were statistically significant differences in OS according to DSS stage (median OS not reached, 73.3 and 47.8 months for stages I, II, and III, respectively; $p < 0.001$), ISS stage (median OS of 79.7, 56.5, and

Table 1 Selected baseline characteristics of patients overall and according to eligibility for transplantation

Characteristics	Transplantation-ineligible patients Value or <i>N</i> (%)	Transplantation-eligible patients Value or <i>N</i> (%)	All patients Value or <i>N</i> (%)
Age	<i>N</i> = 460	<i>N</i> = 390	<i>N</i> = 850
Median (range, years)	68.6 (31.3–97.9)	55 (25.9–73.1)	60.9 (25.9–97.9)
Mean (standard deviation, years)	67.4 (11.2)	54.7 (8.2)	61.6 (11.8)
Sex	<i>N</i> = 461	<i>N</i> = 391	<i>N</i> = 852
Female	233 (50.5)	167 (42.7)	400 (46.9)
Male	228 (49.5)	224 (57.3)	452 (53.1)
Ethnicity	<i>N</i> = 461	<i>N</i> = 391	<i>N</i> = 852
Mixed ancestry, including mulatto	171 (37.1)	185 (47.3)	356 (41.8)
European ancestry	140 (30.4)	103 (26.3)	243 (28.5)
Native American ancestry	44 (9.5)	59 (15.1)	103 (12.1)
African ancestry	32 (6.9)	19 (4.9)	51 (6.0)
Other or unknown	74 (16.0)	25 (6.4)	99 (11.6)
Country of enrolment	<i>N</i> = 461	<i>N</i> = 391	<i>N</i> = 852
Argentina	44 (9.5)	13 (3.3)	57 (6.7)
Brazil	330 (71.6)	347 (88.7)	677 (79.5)
Chile	32 (6.9)	11 (2.8)	43 (5.0)
Mexico	22 (4.8)	0	22 (2.6)
Peru	33 (7.2)	20 (5.1)	53 (6.2)
Monoclonal component	<i>N</i> = 420	<i>N</i> = 376	<i>N</i> = 796
IgG	246 (58.6)	203 (54.0)	449 (56.4)
IgA	102 (24.3)	85 (22.6)	187 (23.5)
IgM	5 (1.2)	2 (0.5)	7 (0.9)
Light chain only	56 (13.3)	75 (19.9)	131 (16.5)
Non-secretory	11 (2.6)	11 (2.9)	22 (2.8)
Bone lesions	<i>N</i> = 436	<i>N</i> = 372	<i>N</i> = 808
Absent	61 (14.0)	33 (8.9)	94 (11.6)
Present	375 (86.0)	339 (91.1)	714 (88.4)
Durie-Salmon stage	<i>N</i> = 434	<i>N</i> = 377	<i>N</i> = 811
I	61 (14.1)	16 (4.2)	77 (9.5)
II	84 (19.3)	91 (24.1)	175 (21.6)
III	289 (66.6)	270 (71.6)	559 (68.9)
International Staging System stage	<i>N</i> = 380	<i>N</i> = 333	<i>N</i> = 713
I	101 (26.6)	108 (32.4)	209 (29.3)
II	135 (35.5)	125 (37.5)	260 (36.5)
III	144 (37.9)	100 (30.0)	244 (34.2)
Creatinine	<i>N</i> = 459	<i>N</i> = 374	<i>N</i> = 833
≤2 mg/dL	336 (73.2)	291 (77.8)	627 (75.3)
>2 mg/dL	123 (26.8)	83 (22.2)	206 (24.7)
Hypercalcemia	<i>N</i> = 428	<i>N</i> = 356	<i>N</i> = 784
Absent	327 (76.4)	268 (75.3)	595 (75.9)
Present	101 (23.6)	88 (24.7)	189 (24.1)

Ig immunoglobulin

33.9 months for stages I, II, and III, respectively; $p < 0.001$), the presence of hypercalcemia (median OS of 61.6 and 31.3 months for patients with and without hypercalcemia,

respectively; $p < 0.001$), and the presence of renal impairment (median OS of 59.0 and 34.1 months for patients with serum creatinine ≤ 2 and > 2 mg/dL, respectively; $p < 0.001$).

Fig. 1 Overall survival of transplantation-ineligible patients (tick marks represent censoring)

Discussion

Paradigm shifts in the treatment of multiple myeloma, such as high-dose chemotherapy rescued by autologous transplantation and the use of immunomodulators and proteasome inhibitors, have allowed for unprecedented improvements in the short- and long-term treatment results for these patients [12]. Unfortunately, transplantation is not feasible in approximately three quarters of the patients, either because of advanced age or comorbidities. On the other hand, the efficacy of immunomodulators and proteasome inhibitors, when used as front-line therapy, has called into

question the role of transplantation even when it is feasible [13]. However, recent interim results from a randomized trial suggest that transplantation should remain a standard of care among eligible patients [14]. Moreover, there is no evidence of decreased utilization of transplantation in the USA and Europe up to 2009/2010 [15, 16]. In addition to transplantation and novel agents, maintenance strategies are also reshaping the approach to multiple myeloma both in the transplantation setting and for transplant-ineligible patients [17–20]. As a result of these improvements, the expected median OS among patients with newly diagnosed multiple myeloma is often close to 5 years among transplant-

Fig. 2 Overall survival of transplantation-eligible patients (tick marks represent censoring)

ineligible patients treated with current regimens [19–22] and typically longer in the transplantation setting [17, 18], in which the adoption of an “optimal strategy” is expected to produce survival rates approaching 80 % at 5 years [12].

To the best of our knowledge, this is the first study including patients with multiple myeloma from several Latin American countries followed prospectively. Unfortunately, not all countries that initially committed to participation were able to enroll patients, and the overall accrual was lower than the expected in some countries. Despite these limitations, we believe our results are representative of the experience of public institutions in Latin America. On the other hand, the Latin American experience at private institutions, where a minority of the population is treated, may well differ from the results reported herein because there is a gap between public and private institutions with regard to the resources that are available for the management of various diseases in Latin America. To our knowledge, the potential prognostic impact of such disparities has not been investigated in this world region for multiple myeloma, but studies in breast and prostate cancer have identified differences in stage at presentation as a possible explanation for worsened outcomes in public institutions in Brazil [23, 24]. Given these features of our world region, we believe it is important to assess treatment results on an ongoing basis, while work continues to be done towards improving access to novel therapies.

The demographic and baseline clinical features of our patients can be contrasted with those reported by Kim et al., who have analyzed 3405 patients from various Asian countries and found a median age of 62 years, 55.6 % of males, serum creatinine <2 mg/dL in 76.6 % of patients, and 44 % of ISS stage III disease [5]. As shown in Table 1, Latin American patients had mostly similar demographic features, but a lower percentage of ISS stage III disease (34.2 %) and somewhat different distributions of other well-known prognostic factors, such as hypercalcemia. Whether these different distributions represent different underlying biology or factors related to the pattern of referral is not clear. It should be noted that the Asian series comprises patients diagnosed between 1986 and 2011, and changes in diagnostic modalities may thus underlie some of the observed differences.

The median age is low, in comparison with published studies, both for our transplant-ineligible (68.5 years) and transplant-eligible (55 years) patients. This finding was already evident in our previous, non-overlapping series [6]. Corresponding medians in published trials ranged between 71 and 72.5 years [22, 25] and between 57 and 58 years [14, 18], respectively. In our study, transplant eligibility was ascertained locally; therefore, there were no centrally determined criteria that could be verified or adjudicated. However, in the investigators’ meeting conducted before data collection, the clinical condition of the patients was agreed upon as a major determinant of transplant eligibility. On the other hand, we have reasons to believe that delayed referral plays a central

role in determining patient fitness in our region, but the extent to which this was indeed the case cannot be ascertained with the available data.

Our OS results for transplantation-ineligible patients (median OS of 43.0 months, with an estimated 5-year OS of nearly 38 %) are within the range reported in the literature for randomized trials among elderly or transplantation-ineligible patients treated with thalidomide-based regimens in the first line [21, 22, 26, 27]. On the other hand, the subsequent addition of bortezomib to the first-line regimen increased the median OS of these patients to 56 months [25]. Notably, many countries have not been able to incorporate some of the novel agents as front-line therapy against multiple myeloma due to cost or local unavailability. Indeed, less than 10 % of patients participating in the current study ever received bortezomib or lenalidomide as a component of therapy after the first relapse. This is the case of Latin American countries, most of which only have thalidomide available at public institutions. Although the similarity between our results and those reported in the literature on thalidomide-based first-line regimens is reassuring, it is conceivable that the outcomes of our patients could be further improved by the availability of novel therapies, to be used in the first line or after disease progression, and which have probably contributed to the OS experience of patients from some of the more recently published trials [28].

Our OS results for transplantation-eligible patients (median OS of 73.6 months) also compare favorably to results reported in the literature, even considering more recent trials [17–19]. Of note is that the median OS was not reached for the subset of patients actually undergoing transplantation, whereas this median was 52.1 months among those who did not receive transplantation. Therefore, it is possible that transplantation of a higher proportion of patients would lead to improved results. In the current study, 45.9 % of patients were initially eligible to autologous transplantation, and only 26.9 % of all patients in fact underwent such procedure. In the Mayo Clinic experience from 2001 to 2010, 37 % of patients with multiple myeloma eventually received an autologous transplantation [28]. It is also noteworthy that only 58.6 % of initially transplantation-eligible patients in fact underwent the procedure. Unfortunately, no data were captured that would allow an assessment of the reasons why individual patients were eventually not treated with transplantation. Nevertheless, the most frequent explanation is likely to be loss to follow-up. In addition, an unduly long time between diagnosis and referral for autologous transplantation has been highlighted as a common problem in Brazil [29]. Thus, earlier diagnosis and referral, as well as increased use of autologous transplantation, could improve patient outcomes, something that remains to be investigated. Moreover, since most novel agents are not yet available at public institutions from many Latin American countries, it is possible that our results could be further improved by the addition of such agents to the therapeutic arsenal.

Our OS results can also be compared with those reported from Asia in a similar, albeit larger, observational study [5]. In that study, 19.8 % of patients with multiple myeloma underwent transplantation, and these patients had a median OS of 79 months. Conversely, the median OS was 41 months for the 80.2 % of patients that did not receive transplantation. In our study, the median survival of transplantation-eligible patients (73.6 months) was longer than that of transplantation-ineligible individuals (43 months), but these two groups represent populations with different prognostic factors. In a landmark survival analysis of transplantation-eligible patients, actual receipt of transplantation before the 12-month landmark had no significant prognostic role in univariable analysis. It should be noted that this analysis is exploratory and observational in nature and does not question the role of autologous transplantation in multiple myeloma.

In recent years, cost has emerged as an overarching concern in the treatment of solid tumors and hematologic malignancies. Cost considerations are especially acute for incurable tumors that mostly affect elderly populations, such as multiple myeloma. Unfortunately, no studies have been published assessing the comparative costs or cost-effectiveness of competing treatment strategies for Latin American patients with multiple myeloma. Given the limited healthcare resources typically found in this world region, especially at publicly funded institutions, further studies should attempt to investigate the comparative merit of the incorporation of novel agents and of increasing the use of transplantation. Both of these strategies will probably be necessary towards moving in the direction of treatment goals that are currently expected in developed countries [12]. A definitive answer to many important questions that remain in the treatment of multiple myeloma can only come from randomized trials; unfortunately, such trials are unlikely to be conducted in a world region where there is comparatively little support for investigator-initiated trials.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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