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EPIDEMIOLOGIA DEL MIELOMA MULTIPLO E CARATTERISTICHE CLINICHE DEI PAZIENTI

Epidemiology of multiple myeloma and clinical characterization of patients

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Abstract
Background Although the epidemiology of multiple myeloma (MM) is widely described, no clinical information is available on Italian MM patients. Having the opportunity to access administrative and clinical sources, this study analysed the characteristics of patients with MM and their pattern of drug use.
Methods A retrospective analysis of an administrative database (ADB) from the Lombardy region (years 2010-2012) was carried out, as well as of a clinical database (CDB) from IRCCS National Cancer Institute (INT) (years 2010-2015). Patients with a first MM diagnosis were identified, and demographic characteristics, MM drug therapies and related treatment lines, and co-morbidities were described.
Results The two analysed databases included 794 (ADB) and 166 (CDB) patients with first diagnosis of MM, respectively. The MM population of Lombardy region had a mean age at diagnosis of 71 years (median 72, range 29-95), and 29% were aged <65 years; mean age was 63 years (median 65, range 34-87) and 55% were aged <65 years for patients attending INT. While in ADB only symptomatic patients could be identified, in CDB 17% of patients were asymptomatic and thus pharmacologically untreated. Twenty-six percent of ADB patients had had prior cardiovascular or renal events (22.7% cardiovascular and 7.9% renal) versus 16% of CDB patients (11.4% cardiovascular and 6.0% renal). In both databases, first-line treatments were multiple therapies based on bortezomib and/or thalidomide; experimental therapies were recorded in 24% of CDB patients. Due to relapse or resistance to therapy, 31% of patients went to a second line in ADB *vs* 38% in CDB, 2% *vs* 11% to third line, and 1% *vs* 11% to fourth or later.
Conclusions MM is confirmed as a disease that affects elderly adults, characterized by quite frequent cardiovascular and renal co-morbidities. The transition to treatment lines after the first one concerns at least one patient in three. The two analyzed databases show differences justified by the younger age and by the use of experimental therapies in the CDB as compared the ADB.

Introduction

Multiple myeloma (MM) is a relatively rare disease, representing about 1% of all cancers and 10% of all hematologic malignancies worldwide [1, 2]. MM is a disease of advanced age: in fact, the median age at diagnosis is 68 years, about 2% of patients at onset is less than 40 old, while 38% of patients are over 70 years [2].
Chromosome 17 deletions are detected in 10% of MM patients at diagnosis and are a hallmark of high-risk MM: these patients have a more aggressive disease, characterized by a shorter time to relapse, extramedullary disease and central nervous system involvement. Deletion of 17p13 is the single most powerful genetic marker for risk stratification [3].
In Italy, MM represents 1.2% of all cancers diagnosed among men and 1.3% among women; MM is more frequent in male subjects, the average incidence being 9.5 cases per 100,000 men every year and 8.1 per 100,000 women. The estimates of the

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AIRTUM (Italian Association of Cancer Registries) indicated in 2006 a total of 2,315 new cases diagnosed among males and 2,098 among females, with fairly homogeneous incidence rates in the country [4]. In 2010, EUCAN (http://eco.iarc.fr/eucan/) - a project of the European Cancer Observatory developed at the International Agency for Research on Cancer - estimated for Italy 2,775 new cases for men and 2.587 for women [5]. The most recent publication AIOM-AIRTUM estimates for 2017 a total of 3,100 new cases diagnosed among males and 2,700 among females [6]. Mortality is slightly decreasing, with an improvement in relative survival: 80% one year from diagnosis, 51% at 5 years from diagnosis, with no differences between genders. The 5-year relative survival recorded an increase of 10 percentage points in fifteen years; however, the impact of the disease on the reduction of life expectancy is relevant, especially in the young patient compared to the healthy subject of the same age and sex: 20 years of life lost if the diagnosis occurs at 50 years of age, 9 years of life lost if the diagnosis occurs at the age of 70. The MM therefore remains a chronic pathology with a poor prognosis in most cases of symptomatic disease [7]. Finally, the estimated prevalence in 2010 was 22,688 subjects, of which only 146 (0.6%) cured, with a regional distribution of MM in line with the distribution of the general population. 59% of prevalent subjects had received the diagnosis of MM in the previous 5 years and 15% more than 10 years earlier [8].

Treatment for MM is indicated in the patient with the presence of symptoms and signs related to the disease [9]. The aim of treatment is to control the pathology, improve the quality of life and survival, which can be achieved by combining effective treatments with adequate supportive care. Until the 2000s, standard therapy for MM was melphalan-prednisolone and vincristine-doxorubicin-dexamethasone regimens [1]. The introduction of new drugs into the MM therapeutic listing (such as bortezomib, thalidomide and lenalidomide, often in combination with dexamethasone) resulted in improved survival, both in newly diagnosed and relapsing patients.

For patients with symptomatic MM younger than 65-70 years of age, with good performance status and without co-morbidities, the therapy of choice is stem cell transplantation (SCT). The procedure involves a first induction phase aiming to reduce the neoplastic mass, a phase of mobilization and collection of stem cells, a conditioning phase and a final phase of re-infusion of the stem cells. The induction phase with bortezomib and lenalidomide (to a lesser extent with thalidomide), in combination with steroids or other chemotherapeutics, has led to an increase in the clinical response compared to traditional chemotherapeutic agents. To promote hematopoietic stem cell collection, cyclophosphamide and growth factors are used as promoters of medullary proliferation. During the conditioning phase, patient undergoes chemotherapy with melphalan, and subsequently the stem cells are reinfused.

For patients not eligible to SCT, first-line therapies are based on bortezomib (often in combination with melphalan and prednisone) or lenalidomide or thalidomide in combination with dexamethasone. Patients with resistance to therapy or relapsing disease are initiated on second line therapy or subsequent lines. In this case 2 or 3 drugs therapy schemes are used: bortezomib in combination with dexamethasone, bortezomib in combination with dexamethasone and liposomal doxorubicin, lenalidomide in association with dexamethasone are rescue therapy schemes already registered since several years in relapsed MM [2].

Beyond what is indicated by the guidelines [2], data on the characteristics of patients with MM and treatment in the clinical practice (real world data) are scarcely available and there are no specific publications on Italian data if not pooled in European multicentre studies [10, 11]. Having the opportunity to access administrative and clinical sources, it was decided to analyse the characteristics and the pattern of use of drugs for Italian MM patients, comparing data of patients treated in an Italian Centre of Excellence for MM and data from a regional administrative database, which includes all treated resident patients.

Methods

We carried out a retrospective analysis on two different sources: an administrative database (ADB) from the Lombardy region containing data of resident patients in the region (years 2010-2012), and a clinical database (CDB) of the IRCCS National Cancer

Institute (INT) Foundation containing data of patients attending the Department of Hematology (years 2010-2015). In both cases, patients with a first diagnosis of MM were identified, and demographic characteristics, MM drug therapies and use patterns were described. Given the high frequency of co-morbidities in MM patients [12] and given their relevance in determining their eligibility for SCT, analyses were also performed in patients with previous cardiovascular and renal events.

Administrative database (ADB) analysis

Lombardy region covers around 10 million people. Administrative databases include: demographic data, hospital discharges, pharmaceutical prescriptions, and outpatient claims. Retrospective analysis of a Lombardy regional database was conducted first to evaluate the treatment of patients admitted to hospital with a diagnosis of MM. The information contained in the regional databases were analysed to establish the clinical characterisation of MM patients, highlighting age, sex, renal and cardiovascular comorbidity, and to evaluate the treatment pattern of patients admitted to hospital for MM. The retrospective analysis focused on the following cohort characteristics: cardiovascular and renal co-morbidities as well as exposure to treatment.

All patients admitted to hospital in 2010 with a principal or secondary MM diagnosis (ICD-9, 203.00) were selected. The date of discharge after the first admission for MM during the period (index hospitalisation) was the "index date".

The following patients were excluded:

i) those not resident in Lombardy;
ii) those admitted to hospital with a haematopoietic tumour (ICD-9 200.XX-208.XX) in the 10 years prior to the index date;
iii) those who died during the index hospitalisation;
iv) those whose treatment did not begin with one of the drugs of interest.

Each member of the cohort was monitored from the index date until the date of death, emigration or end of follow-up (31.12.2012), whichever was the earliest.

To evaluate prior history of renal events and heart disease in the patients included in the cohort, we recorded whether the patients had been hospitalised at least once with a principal or secondary diagnosis of kidney disease (ICD-9 584.XX, 585.XX, 586.XX) or heart disease (ICD-9 410.XX-414.XX, 420.XX, 423.XX-429.XX) in the 10 years prior to entry into the cohort.

The following drugs were considered to be of interest for the analysis:

- Cyclophosphamide (ATC L01AA01)
- Melphalan (ATC L01AA03)
- Bendamustine (ATC L01AA09)
- Vincristine (ATC L01CA02)
- Doxorubicin (ATC L01DB01)
- Bortezomib (ATC L01XX32)
- Thalidomide (ATC L04AX2)
- Lenalidomide (ATC L04AX4).

All the oncological drugs of interest administered during the follow-up were identified from the hospital's pharmaceutical database (file F). Beginning with the first-line treatment (first drug administered), if the next administration was tried less than 8 months after the first, patients were classified into two groups depending if (i) they received the same drug, or (ii) the patient received a different drug.

Clinical database (CDB) analysis

The database of the Department of Hematology of IRCCS Foundation - National Cancer Institute (INT) of Milan was analyzed. The original data were anonymous, identified only by an alphanumeric code. The entire database population diagnosed from MM between 2010 and 2015 has been analysed.

Assessed variables:

- date of birth
- sex
- date of diagnosis of MM
- co-morbidities recorded at diagnosis
- received medicines

• start and end date of each therapeutic line received from patient
• deletions of chromosome 17

Cardiovascular events were already recorded into the database. Renal failure was identified by creatinine value was >2 mg/dL.

Statistical analysis

The analyses on the two databases (ADB and CDB) were descriptive and were performed using SAS statistical software (SAS Institute Inc., Cary, NC, USA).

Results

In 2010, 2,263 patients were hospitalised for MM in Lombardy. 152 patients were excluded because they were not resident in the Lombardy Region, 1,266 because they had previously been hospitalised with a diagnosis of haematopoietic cancer, and 51 because they died during the index hospitalisation. The final cohort consisted of 794 patients with a first admission for MM in 2010, who were resident in the Lombardy and alive at the end of the hospitalisation period. In the treatment pattern analysis, the cohort was limited to 334 patients, as no information about post-admission treatment was available for 298 patients, and a further 162 did not begin treatment with one of the drugs of interest.

All 794 patients included into the cohort have been analysed to describe main characteristics. Demographic data are shown in **Table 1**. Subjects' mean age was approximately 71 years (median 72, minimum 29 - maximum 95) and about 30% of patients were less than 65-years old. There was no difference in gender distribution (49.5% males *vs* 50.5% females). In 7.9% of subjects there was at least one hospitalization for renal event (acute or chronic renal failure) in the 10 years preceding the first admission for MM, while 22.7% of patients had at least one heart disease event (coronary artery disease, cardiomyopathies, arrhythmias, heart failure or other heart conditions). A total of 209 patients (26.31%) had been admitted to hospital with a diagnosis of heart disease or renal disease in the 10 years prior to admission for MM. Of the 794 patients included in the cohort, 6.4% died within one month of discharge while 73.1% had survival longer than one year (**Table 1**). Regarding treatments following the admission for MM, only 334 were treated with drugs of interest.

Table 1 Frequency distribution of demographic characteristics of cohort subjects included in the administrative database of the Lombardy region, Italy.

Subjects, N			**794**
Sex, N (%)		M	393 (49.5)
		F	401 (50.5)
Age at diagnosis (years)	Mean ± SD		70.66 ± 11.13
	Median (min–max)		72 (29-95)
Age classes at diagnosis (years), N (%)		<60	139 (17.51)
		60-64	94 (11.84)
		65-69	110 (13.85)
		70-74	156 (19.65)
		75-79	145 (18.26)
		≥80	150 (18.89)
Survival (days), N (%)		≤30	51 (6.42)
		31-60	35 (4.41)
		61-180	71 (8.94)
		181-365	57 (7.18)
		≥365	580 (73.05)
Comorbidities, N (%)		Hospitalisation for renal event	63 (7.9)
		Heart disease event	180 (22.7)
		Hospitalisation for heart or renal disease	209 (26.3)

Primarily, the frequency distribution of the initial treatment was evaluated (i) on the entire cohort and (ii) after stratifying for the presence or absence of kidney or heart disease prior to admission to the cohort. In the cohort at a whole (334 patients), almost all began treatment with bortezomib (67.4%) or thalidomide (20.1%) or lenalidomide (9.3%). The same distribution is obtained by stratifying for the presence or absence of prior heart or kidney disease. Of those 334 patients, 28 had a single prescription, 201 had more than one prescription and did not change treatment line during the follow-up, the remaining 105 (31.4%) had one or more line changes. In the cohort of 70 patients with cardiovascular-renal comorbidity, 44 had a single prescription or did not change treatment line, 25 had one change of line, and 1 had 2 changes of line (patients changing one or more lines: 37.14%). The frequency distribution of treatment line changes on the whole cohort and after stratification for prior kidney and heart disease is reported in **Table 2**. Of those who changed treatment, 93 (27.8%) only had one change of treatment and 9 (2.7%) only 2, while 3 (0.9%) had 3 or more. Patients with prior kidney disease seemed to have a higher propensity towards a treatment line change *vs* patients with heart disease (35.7% *vs* 25.7%), although the difference was not significant (z test p-value 0.058).

Table 2 Frequency distribution of treatment lines and adverse events.

Number of changes, N (%)	Total N=334	Cardiovascular or renal event	
		No N=264	Yes N=70
0*	229 (68.56)	185 (70.07)	44 (62.86)
1	93 (27.84)	68 (25.76)	25 (35.71)
2	9 (2.69)	8 (3.03)	1 (1.43)
3 or more	3 (0.91)	3 (1.14)	0 (0.00)

** 28 of these patients had only one available prescription.*

Frequency distributions of changes from first- to second-line treatment for the entire cohort is shown in **Table 3**. Most frequent changes were from thalidomide to bortezomib (29.9%), bortezomib to lenalidomide (27.1%) and lenalidomide to bortezomib (25.8%).

Table 3 Frequency distribution of changes to second-line treatment in the cohort of the administrative database of the Lombardy region, Italy.

		Second-line treatment									
	N (%)	Cyclopho-sphamide	Cyclophosphamide and vincristine	Vincristine	Cyclophosphamide and bortezomib	Melphalan	Melphalan and bortezomib	Bortezomib	Thalidomide	Lenalidomide	Total
First-line treatment	Cyclophosphamide	3 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (0.0089)
	Cyclophosphamide and vincristine	0 (0)	3 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (0.0089)
	Vincristine	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Cyclophosphamide and bortezomib	0 (0)	0 (0)	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.0029)
	Melphalan	0 (0)	0 (0)	0 (0)	0 (0)	1 (33.33)	0 (0)	1 (33.33)	1 (33.33)	0 (0)	3 (0.0089)
	Melphalan and bortezomib	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)	1 (0.0029)
	Bortezomib	0 (0)	0 (0)	1 (0.44)	0 (0)	0 (0)	0 (0)	155 (68.89)	8 (3.56)	61 (27.11)	225 (0.67)
	Thalidomide	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	20 (29.85)	42 (62.69)	5 (7.46)	67 (0.2)
	Lenalidomide	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	8 (25.81)	0 (0)	23 (74.19)	31 (0.092)
	Total	3 (100)	3 (100)	1 (0.44)	1 (100)	1 (33.33)	1 (100)	184 (157.88)	51 (99.58)	89 (108.76)	334

The first-line treatments are shown in the rows and the second-line treatments in the columns. The diagonal shows the patients with no change of line.

In the clinical database from INT, 166 patients were diagnosed between 1st Jan 2010 and 31st Dec 2015, of whom 17% were asymptomatic, more males (54.2%) than females. The mean age at diagnosis was 63 years (median: 65; minimum 34 - maximum 87) and 93 patients (56.0%) were less than 65 years old (**Table 4**).
Given the database structure, 1-year survival could not be evaluated. However, on 31st Dec 2015, 84% of patients were alive, having on average 2.89 years from diagnosis date. About 16.3% of 166 patients had cardiovascular and/or renal comorbidities. 19 (11.5%) had been hospitalised at least once for one of the cardiovascular comorbidities: 9 patients for arrhythmias, 9 patients for coronary heart disease and 1 for stroke (cases of hypertension, thrombosis and valve defects were excluded). Renal failure was diagnosed in 10 patients (6.0%) while patients with both cardiovascular and renal comorbidity amounted to 1% of total patients (**Table 4**). Chromosome 17 deletion was analysed on a sample of 111 patients who underwent the cytogenetic test, and 11 patients (9.91%) presented chromosome 17 deletion.
As in **Table 4**, 38% of treated patients had one or more changes (*vs* 31% in ADB). 85 patients (61.6%) received a first-line therapy and did not change it during the follow-up, the remaining 53 had one or more line changes: 23 (16.7%) only had one change of treatment, 15 (10.9%) two changes, while 15 (10.9%) had 3 or more. The most frequent changes were from bortezomib to lenalidomide and *viceversa*, thalidomide to bortezomib, experimental drugs (carfilzomib, ixazomib) to lenalidomide.

Table 4 Frequency distribution of demographic characteristics of cohort subjects from the clinical database from the National Cancer Institute, Milan, Italy.

Subjects			**166**
Sex N (%)		M	90 (54.22)
		F	76 (45.78)
Age at diagnosis (years)	Mean ± SD		63.01 + 11.65
	Median (min –max)		65 (34-87)
Age classes at diagnosis (years)		<60	62 (37.50)
		60-64	29 (17.50)
		65-69	27 (16.25)
		70-74	24 (14.38)
		75-79	7 (4.38)
		≥80	17 (10.00)
Number of changes for treatment lines N (%)		0	85 (61.59)
		1	23 (16.67)
		2	15 (10.87)
		3	15 (10.87)
Comorbidities N (%)		Cardiovascular or renal disease	27 (16.27%)
		Hospitalisation	19 (11.45%)
		Arrhythmia	9 (5.42%)
		Coronary heart disease	9 (5.42%)
		Stroke	1 (0.60%
		Renal failure	10 (6.02%)

The analysis of the first-line treatment, conducted on the whole sample of 166 patients, found first that asymptomatic patients (28, 16.9% of whole sample) were not treated, as recommended by guidelines. Of 138 patients receiving a first-line treatment, 76 patients (55.1%) received a bortezomib-based regimen, while 23.9% of patients received an experimental therapy (**Table 5**).

Table 5 First-line treatments.

		N (%)
Total patients		**166 (100)**
Untreated (asymptomatic patients)		28 (16.9)
Treated patients		138 (83.1)
of whom, regimen with:	Bortezomib	76 (55.1)
	Talidomide	5 (3.6)
	Lenalidomide*	23 (16.6)
	Carfilzomib**	7 (5.1)
	Ixazomib**	3 (2.2)
	Others	23 (16.7)
	NA	1 (0.7)

** first-line experimental therapy until 2016*
*** experimental therapy*

Discussion

This real world study on management of MM patients in two representative realities, one of the general population and the other one of centres of excellence, adds new information to what is publicly available, with differences between the two examined populations that deserve a detailed analysis.

The study confirms that MM is a disease affecting adults of both sexes, slightly more frequently in males, and in old age. However, the analysis highlighted a rather marked difference: while the mean age of ADB patients (71 years) is in line with what reported in the literature [2, 4, 7, 8], the mean age of patients attending the Department of Hematology of the National Cancer Institute (INT) is much lower (63 years). Considering that age below 65-70 is a criterion of eligibility for SCT and that INT is a reference centre in Italy for transplantation, we could explain the relative young age of CDB patients with patients transplanted or in induction therapy.

Differences between the two populations also emerge in relation to co-morbidities. ADB patients have a higher cardiovascular and renal disease rate (26%) than CDB patients (16%). Also in this case the difference in age between the two groups could explain this further difference. Moreover, given that important comorbidities such as cardiovascular and renal are exclusion criteria for transplantation, it is likely that the INT population is *a priori* selected.

In the clinical practice, first-line and subsequent therapy for MM is in line with recommendations made by scientific guidelines [2], preferring bortezomib-based regimens. It is interesting to note how the thalidomide-based regimens (with a lower tolerability than lenalidomide) are less frequent in CDB patients where a high rate of experimental therapies (24%) has been recorded. At least one patient out of three goes to treatment lines after the first, indication of a relapsing disease: 31% of patients in the ADB changed two or more treatment lines *vs* 38% of CDB patients. To explain this difference, it can be hypothesized that patients referring to INT are more severe than the average. Drugs that are used in the subsequent lines are also in line with recommendations of guidelines [2].

It was not possible to compare survival between the two populations but still interesting to examine the one-year net survival of ADB patients (73%) compared to what was recently published by AIRTUM (80%) [7]. This difference could be explained by the absence of asymptomatic patients in the ADB (considered instead in the tumour registries) and by AIRTUM more recent data (while the ADB analyses 2010-2012 years).

The most important limitation of this study lies in the different structure of the two databases that did not allow a complete comparability of the two populations and the patterns of drug use. In addition, the ADB, like any administrative database, does not allow identifying asymptomatic patients, with the loss of information on a potentially large sample. Finally, transplants were not analysed as non-pharmacological treatment; however, the analysis would provide relevant information on the real-life management of the patient with MM, since it is the treatment of choice for patients under age 70.

MM is confirmed as a disease that affects elderly adults, with cardiovascular and renal co-morbidities quite frequent. The transition to treatment lines after the first one concerns at least one patient in three, a sign of a disease that relapses, despite the new generation therapies. The two databases analysed show differences justified by the younger age and by the use of experimental therapies in patients attending a research centre.

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