How to treat multiple myeloma – a representative multicentre treatment survey

Repräsentative multizentrische Erhebung zur Behandlung des multiplen Myeloms

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Aim: The present survey was undertaken to gain insights in the changes of disease management of multiple myeloma (MM) over time and the implementation of new guidelines into daily practice.

Patients and methods: Diagnosis and treatment of MM were evaluated based on a representative multicentre survey including 386 patients from 35 centres in Germany in 2008. The results were compared to similar surveys in 2004 and 2006.

Results: At the time of first diagnosis most patients (62.5%) were already in stage III (Durie-Salmon). The presence of deletion 13q was determined in 22% of patients only. However, determination of other prognostic factors has become increasingly well established. These include the levels of $ß_2$-microglobulin and serum albumin, each of which was determined in more than 2/3 of patients. Overall 35% of patients were considered for high dose chemotherapy. As a consequence of the development of innovative substances, there are remarkable shifts in first line, second line and third line therapy with an increase in the use of bortezomib at all levels of therapy.

Conclusion: Regarding diagnostic measures deviations from recommended guidelines became evident. Also, high dose chemotherapy was considered in a minority of patients only. Novel substances, however, were rapidly integrated into the treatment of MM.

Keywords: multiple myeloma, diagnosis, therapy, treatment survey

Ziel: Im Rahmen der vorliegenden Erhebung sollten Einsichten in Veränderungen der Behandlung des multiplen Myeloms und die Implementierung von Leitlinien gewonnen werden.

Patienten und Methoden: In einer repräsentativen multizentrischen Erhebung in 35 Zentren wurden Diagnostik und Therapie des MM bezogen auf einen Zeitraum von drei Monaten (1. Quartal 2008) anhand der Daten von 386 Patienten ausgewertet. Dies wurde mit den Resultaten vorangegangener Erhebungen von 2004 und 2006 verglichen.

Ergebnisse: Die meisten Patienten (62.5%) waren zum Zeitpunkt der Erstdiagnose bereits im Stadium III (nach Durie-Salmon). Nur bei 22% der Patienten wurde das Vorhandensein einer Deletion 13q überprüft. Allerdings hat sich die Bedeutung anderer Prognosefaktoren wie beispielsweise ß2-Mikroglobulin und Serum-Albumin mehr und mehr etabliert (Messung jeweils bei über 2/3 der Patienten). Insgesamt waren 35% der Patienten für eine Hochdosischemotherapie vorgesehen. In der Erst-, Zweit- und Drittlinientherapie ist es durch die Entwicklung innovativer Subtanzen zu erheblichen Verschiebungen gekommen. Auffällig war eine zunehmende Verwendung von Bortezomib über alle Therapiestufen.

Schlussfolgerung: Hinsichtlich der Diagnostik zeigen sich im Detail Abweichungen von internationalen Empfehlungen. Weiterhin wird nur bei einer Minderheit der Patienten eine Hochdosischemotherapie mit Stammzellsupport durchgeführt. Andererseits wurden neue Substanzen schnell nach ihrer Zulassung in die Myelomtherapie integriert.

Schlüsselwörter: Multiples Myelom, Diagnostik, Therapie, repräsentative Erhebung

Introduction

Multiple myeloma (MM) is a malignant lymphoproliferative disorder of terminal differentiated B cells.[1;2] It is characterised by a diffuse and/or multilocular infiltration of the bone marrow by monoclonal plasma cells. Osteolysis and suppression of haematopoesis (lead symptom: anaemia), renal insufficiency and hypercalciaemia are the main symptoms.[3] MM develops from an asymptomatic and pre-malignant plasma cell proliferation, without end-organ damage, designated as "monoclonal gammopathy of undetermined significance" (MGUS).[3;4]
The incidence of MM is approximately 4–6/100 000/year, with a median age at first diagnosis of between 63 and 70 years[4;5] and with 65% of the patients aged over 65 years.[6]

Diagnosis should be based on blood and urine tests and bone marrow biopsy / aspiration, as well as X-rays and other imaging tests. In more detail, the identification of a monoclonal component in the serum and/or urine, the quantification of the immunoglobulins, the characterisation of the heavy and light chains by immunofixation, together with serum-free light-chain measurements form the basis to define the type of MM and to monitor the course of the disease.[5;7] Diagnostic criteria to discriminate MGUS from asymptomatic myeloma and from symptomatic myeloma, respectively, are summarised in Table 1.

The staging system according to Durie and Salmon (Table 2) is of importance for giving a rough estimate of the tumour cell mass at the time of the diagnosis.[8;9] For many years it formed the basis to decide upon initiation of treatment. However, the International Staging System (Table 2) is a more convenient and reproducible classification.[5;9;10] While systemic therapy is an internationally accepted treatment for stage III disease, there was (and still is) no need for systemic therapy in stage I. In stage II disease, however, treatment should be offered if end organ damage is found. Today, evidence of organ damage due to MM (CRAB criteria, see below) defines the indication to commence specific treatment.

Biological parameters predict the clinical course and prognosis of MM. A poor prognosis is linked to increased levels of $ß_2$-microglobulin and/or decreased levels of serum albumin. The most relevant cytogenetic abnormalities with prognostic importance - obtained by conventional karyotyping or fluorescent in situ hybridization (FISH analysis) - are del(13q), t(4;14) and del(17p); the detection of these factors is associated with a poorer outcome.[5] By FISH specific genetic changes in interphase cells can be detected, overcoming the problem of lack of dividing cells required to obtain conventional cytogenetics.[11]

Initial treatment should be started in patients with symptomatic MM according to the definition of the International Myeloma Working Group, i.e. at least one of the CRAB-criteria (**c**alciaemia, **r**enal insufficiency, **a**naemia and **b**one lesions). Asymptomatic patients with rapidly progressive disease and the risk of complications are also treated. The most important treatments are chemotherapy combined with glucocorticoids and – to an increasing degree – bortezomib, thalidomide and its derivate lenalidomide. High-dose chemotherapy followed by autologous stem cell transplantation is considered the treatment of choice for younger patients up to 70 years of age.[5] Allogeneic stem cell transplantation may be considered for the subgroup of physically fit patients with poor prognostic features, however, this therapeutic procedure is a matter of an ongoing debate. Therefore, it should be applied only under conditions of a controlled clinical trial.[4] Radiation therapy is used for local tumour control and to reduce bone pain. Supportive care consists of bisphosphonates, analgetics, blood transfusions, and the substitution of erythropoietin.[5;12] In the past, most patients with MM died within 2 to 4 years of diagnosis. In the last decade, the introduction of new therapeutic interventions – including stem cell transplantation, bortezomib, thalidomide and lenalidomide – has increased long-term survival rates. The relative survival values of patients with MM in the United States for the periods 1990-1992 and 2002-2004 were compared, on the basis of data taken from the 1973-2004 database of the Surveillance, Epidemiology, and End Result (SEER) Program. Comparison of the values showed that the 5-year survival increased from 28.8% to 34.7% ($P<0.001$) and the 10-year survival increased from 11.1% to 17.4% ($P<0.001$).[13]

Methods

The aim of this retrospective survey was to analyse treatment patterns in multiple myeloma (MM) in Germany within a three months time period in 2008 with respect to previously identified prognostic markers and the availability of new effective drugs. The results were compared to similar surveys from the years 2004 and 2006 (for details see Table 3).

The analysis is based on an epidemiological database (TherapyMonitor by OncologyInformation Service, Freiburg) including 386 patients from 35 centres in Germany, constituting a representative statistical sample regarding the distribution of the treated prevalence in MM (5 university hospitals, 16 community hospitals, 14 office-based haematologists).

The selection of the centres was based on a two-step procedure. A total of 800 institutions involved in the treatment of malignant haematological diseases in Germany were contacted by mail. The response rate was 15 %. In conclusion, the "treated prevalence" of patients with MM in Germany was determined as follows: university hospitals 14%, community hospitals 46%, office-based haematologists 40%. Then, the target population was defined considering the type of treatment centre and distributed regionally taking into account the population density. Finally, the respective centres were selected according to the date of response to the mailing.

Data from patients with MM were reported and analysed retrospectively. The inclusion criterion was that any therapeutic decision - start, change or end of therapy – was taken within the first quarter 2008. An external and onsite monitoring system assessed plausibility and correctness of the data. The results were compared to similar surveys in 2004 and 2006. Changes over time in diagnostics and treatment patterns were analysed in the entire patient group as well as in subgroups according to age (cut-off 65 years), Karnofsky performance index (KI), and institution (university hospitals, community hospitals, office-based haematologists), respectively.

Statistical analysis: The analyses presented in this paper are explorative. Differences in the treatment patterns or the use of cytostatic drugs in different subgroups were evaluated by means of a two-sided Chi-square test. A p-value of less then 0.05 was considered statistically significant.

Results

Details of the representative sample

The representative multicentre treatment survey was based on 35 centres with 386 patients. The centres participating were 14% university hospitals, 46% non-university hospitals and 40% office based oncologists. 75% of the patients were at least 60 years old when the diagnosis was first made and 25% were aged 30 to 59 years. 66% of the diagnoses were made in patients aged 60 to 79 years and 9% of the diagnoses in patients aged 80 years or higher. The 386 patients included 227 male and 159 female patients. This corresponds to the gender distribution given in the literature and - together with the age distribution - indicates that the sample is representative [9].
Age distribution differed between university hospitals, non-university hospitals and office based haematologists. Whereas 47.5% of the patients in university hospitals were younger than 65 years, the corresponding figures for non-university hospitals and office based haematologists were 41% and 34%, respectively.

Diagnosis of MM

Most patients were already in Durie-Salmon stage III at the time of the initial diagnosis - 62.5% stage III, 20.6% in stage II and 16.9% in stage I. Corresponding to this, the great majority of patients were symptomatic at the time of diagnosis. Most frequently reported symptoms were weakness (36%), tiredness (39%), loss of energy (39%), and bone pain (43%). 14% of patients already suffered from bone fractures. The tentative diagnosis of MM was mostly made in non-university hospitals (61%), followed by office-based haematologists (22%) and university hospitals (18%). A similar distribution was found for confirmation of the diagnosis. There was a trend that more patients are being diagnosed in non-university hospitals (61% in 2008 vs. 51% in 2004).

Defining the risk profile

22% of all patients were tested for the presence of the deletion 13q by FISH. The FISH-based detection of the deletion was performed in only 18% of patients in university hospitals and office-based haematologists, but in 28% of patients in non-university hospitals.

In a total of 81 patients chromosomal abnormalities were detected: del(13q) in 56%, t(4;14) in 12%, and del(17p) in 8%, respectively. In 24% of the patients, a broad variety of other cytogenetic abnormalities was documented. The $ß_2$-microglobulin was measured in 72% of patients. The application of this test has risen over the years: in 2004 in 27% of patients and in 2006 in 58% of patients ß2-microglobulin was determined. Analysis by centre showed that mainly university hospitals (89%) and non-university hospitals (70%) recognised the prognostic significance of $ß_2$-microglobulin, while only 53% of office-based haematologists performed this test. Albumin was determined in 72% of patients. Here too, predominantly university hospitals (89%) and non-university hospitals (69%) applied this analysis - in comparison to 47% of office-based haematologists. In all of these patients albumin was determined in the serum, whereas proteinuria was measured in a small minority (8%) of patients only.

Concomitant diseases

While the majority of patients aged under 65 years had no documented concomitant disease (54%), only 28% of patients aged over 65 had no concomitant disease. The concomitant diseases found in patients aged over 65 years included the age-related conditions like hypertension (37% versus 22% in the younger), chronic heart failure (20% versus 3%) and diabetes mellitus (12% versus 6%), as well as renal insufficiency defined according to local standards (22% versus 12%).

Therapy of MM

Primary treatment was mainly initiated in non-university hospitals (57%), followed by university hospitals (23%) and office-based haematologists (20%). Primary therapy was then continued in these institutions in a similar proportion. Onset of treatment based on the CRAB criteria in 35% of therapeutic decisions only. But, primary therapy was initiated in 87% of MM patients upon diagnosis. 48% of patients in stage I and 95% of patients in stages II or III, respectively, were treated. The types of first line treatments are depicted in Figure 1. The initiation of chemotherapy in stage I was independent of age, general condition and renal disease. Analysis by type of centre showed that office-based haematologists applied chemotherapy (with or without radiotherapy) in 70% of

patients with stage I disease, followed by non-university hospitals (65% of stage I patients) and university hospitals (45% of stage I patients).
In first line, 24% of patients were treated within clinical trials. This proportion has increased over the years (15% in 2004, 16% in 2006). Most of these patients were treated in university hospitals (40%), followed by non-university hospitals (24%) and office-based haematologists (11%).

First line therapy

Agents applied in primary conventional chemotherapy were mainly dexamethasone (58%), prednisone (31%), melphalan (29%), adriamycin (29%) and vincristine (25%) (multiple entries possible). Comparison between the years 2006 and 2008 showed a clear trend towards the greater use of new substances (Table 4, Figure 2). Treatment choice was influenced by the general condition of the patients although a statistical significance could not always been demonstrated. When looking at patients with a KI <90% or ≥90% differences became apparent for melphalan +/- steroids (21% vs. 8%, p=ns), bendamustine based therapies (9% vs. 4%, p=0,12) and dexamethasone monotherapy (6% vs. 2%, p=0,001). Bortezomib based therapies were administered more often in patients with a KI above 90% (22% vs. 7.3%, p=0,001). The use of VAD-like regimens was similar in both groups. Major differences became apparent between the types of centre with regard to the substances used. VAD-like regimens were predominantly administered in university hospitals and non-university hospitals, whereas office-based haematologists preferred melphalan and bendamustine (each in combination with a steroid). Also, while not approved at the time of this survey, first-line lenalidomide was used almost exclusively in university hospitals. Only minor differences between the institutions, however, were found regarding the usage of bortezomib.
A detailed analysis of the first-line treatment behaviour is depicted in Figure 3.

High dose chemotherapy

In 2006, 33% of the institutions gave an affirmative answer to the question about the planning or implementation of high dose chemotherapy with stem cell support, in comparison to 35% in 2008. Interestingly, the number of autologous transplants is

increasing over time in favour of the non-university hospitals. The proportion of high dose chemotherapy in the different institutions and according to age is depicted in Figure 4.

Termination of first line therapy

Primary therapy was ended in 46% of the patients after maximal response and in 23% once a plateau phase had been reached. In an additional 18% of patients, relapse or progression of the disease led to termination of the primary therapy. Primary therapy was terminated in 7% of cases following the patient's wishes and in only 3% of patients due to side effects, other reasons led to termination in 16% (multiple entries possible).

Supportive care

The use of supportive therapy in primary therapy has continuously increased in recent years. 71% of patients were treated with bisphosphonates. Other frequently administered supportive interventions were pain treatment (2008: 72%; 2006: 52%), followed by erythrocyte concentrates (2008: 61%; 2006: 40%) and antibiotics/ antifungal drugs (2008: 55%; 2006: 33%).

Second line therapy

The reason for secondary therapy in first relapse or progression (period of first remission: mean 19 months, median 12 months) was the detection of an increasing M-gradient in 71% of patients, the occurrence of new osteolysis in 49% of patients, development of anaemia / leukopenia / thrombocytopenia in 30% of patients, and the diagnosis of renal insufficiency in 16% of patients. Secondary therapy was mainly performed in non-university hospitals (2004: 46%; 2006: 57%; 2008: 52%) and by office-based haematologists (2004: 27%; 2006: 22%; 2008: 32%). The proportion of patients treated in university hospitals after the first relapse or progression is decreasing (2004: 31%; 2006: 24%; 2008: 17%). In 2004 dexamethasone was most frequently used, followed by melphalan and prednisone. Although bortezomib played only a minor role in 2004, it was increasingly used in the following years (Figure 2). Since the use of thalidomide was declining, lenalidomide based therapies seem to gain importance. Bendamustine was chosen increasingly, whereas the choice for melphalan +/- steroids

decreased. Although administered less frequently over time, VAD-like regimens still play a considerable role in the treatment of first relapse (18% in 2006 and 10% in 2008).

There was a (statistically not significant) trend to prescribe bortezomib and thalidomide particularly in younger patients (under 65 years) and in patients with a KI ≥ 80. Older patients, in contrast, were more often given bendamustine (p=0,02). There was no relevant difference concerning age and performance status for lenalidomide. Details of second line treatment and changes over time are depicted in Table 4.

Third line therapy

If systemic therapy is required in second relapse, this was mostly performed by office-based haematologists (58%), followed by university hospitals and non-university hospitals (each 25%) (multiple entries possible). The most frequently used drugs were dexamethasone (52%) and bortezomib (40%). The frequency of the different treatment regimens are shown in Table 4. Bortezomib was used regardless of age, but predominantly in patients with good general condition. Lenalidomide was preferred for younger patients in good general condition. Bendamustine was more frequently prescribed in older patients with a KI < 80%.

Conclusions

The biological basis of multiple myeloma remained the same; however, new diagnostical tools and therapeutical interventions have been introduced and the changes in the management of the disease have shown a clear benefit in terms of survival in younger patients.[13]

The aim of this survey was to provide insights in the changes of disease management and – indirectly – the implementation of guidelines into daily practice.

Some distinctive features have become apparent.

First, the reason to treat such a high proportion of patients with stage I disease remains unclear. There is no data showing that these patients had special features such as advanced organ involvement like renal failure or low Karnofsky performance status. In general, systemic treatment of patients with stage I disease contravenes against international recommendations.[5]

Interestingly, a wide use of bisphosphonates in stage I becomes obvious even though this is not in accordance with current guidelines. A possible explanation may be that the treating physicians feel prompted to initiate bisphosphonate therapy due to a considerable proportion of patients suffering from co-existing osteoporosis. But, unfortunately, the data set does not allow verifying this hypothesis.
Assessment of risk factors developed heterogeneously during the observation period of this survey. ß2-microglobulin gained acceptance, but FISH analysis was performed in 22% of the patients only. The rate was even low in university hospitals. Up to now there is no accepted algorithm to stratify treatment according to cytogenetic abnormalities. However, it is strongly recommended to assess cytogenetic risk factors within clinical trials in order to generate a basis for risk adapted treatment stratification in the future. Since allogeneic stem cell transplantation does not appear feasible for broad application in high-risk patients, there is urgent need to develop new options for patients with poor prognostic features. The novel substances were established rapidly in the treatment of MM. The treatment of choice seems to be influenced by factors like age and Karnofsky performance status. Older patients are more often treated with conventional substances like bendamustine or melphalan. Nevertheless, increasing evidence exists for the beneficial use of novel agents in elderly patients.[12]
The proportion of patients receiving vincristine-based regimens is still remarkably high (25% in first line and 10% in second line). The value of this substance has often been questioned, since it does not add to the outcome rates achieved with dexamethasone alone.[14;15]
High dose chemotherapy in first line was considered for a minority of the patients only (35%). This reflects the proportion of patients below the age of 65 years (40%). Nevertheless, convincing data showed the applicability of intermediate-dose melphalan followed by peripheral stem cell support in elderly patients. Therefore, this procedure is recommended by current IMWG guidelines[12] in patients aged 65-70 years whenever full-dose melphalan is considered too toxic.

In summary, this survey showed the rapid implementation of new substances like bortezomib, thalidomide and lenalidomide into routine therapy. Such type of analysis across the different facilities involved in the treatment of patients with MM may contribute to calculate the resources needed. It may also allow to detect deviations or

even deficiencies with respect to recommended guidelines. Finally, it describes daily clinical routine.

Conflict of Interest

Wolfgang Knauf: Advisory board (Janssen-Cilag, Celgene, Mundipharma)

Lenka Kellermann: Honoraria (Janssen-Cilag GmbH)

Wolfgang Poenisch: none

Hermann Einsele: Speaker's Bureau (Janssen-Cilag, Novartis, Celgene)

Christian Straka: none

Claas Frohn: Employment (Janssen-Cilag GmbH)

Hartmut Goldschmidt: none

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MGUS	Asymptomatic (smoldering) myeloma	Symptomatic myeloma
M-protein in serum <30 g/l Bone marrow clonal plasma cells <10% and low level of plasma cell infiltration in a trephine biopsy (if done) No evidence of other B-cell proliferative disorders No related organ or tissue impairment (no end organ damage, including bone lesions)	M-protein in serum ≥ 30 g/l and/or Bone marrow clonal plasma cells ≥10% No related organ or tissue impairment (no end organ damage, including bone lesions) or symptoms	M-protein in serum and/or urine Bone marrow (clonal) plasma cells or plasmacytoma Related organ or tissue impairment (end organ damage, including bone lesions)

Table 1 Diagnostic criteria for MGUS, asymptomatic myeloma and symptomatic myeloma [6]

Durie-Salmon Criteria			
Parameter	**Stage I** **All of the criteria below**	**Stage II**	**Stage III** **One or more of the criteria below**
Haemoglobin	> 10 g/dl	Neither stage I nor stage III	< 8.5 g/dl
Serum calcium	< 2.6 mmol/l		> 3.0 mmol/l
Bone structure	normal bone structure or solitary bone neoplasm only (bone x-ray)		Advanced bone lesions
M-Protein IgG IgA Bence Jones Protein	 < 50 g/l (serum) < 30 g/l (serum) < 4 g/24 h (urine)		 > 70 g/l (serum) > 50 g/l (serum) > 12 g/24 h (urine)
Subclassification	Stage A	Serum creatinine	< 178 µmol/l
	Stage B	Serum creatinine	> 178 µmol/l
ISS Criteria			
	Stage I	**Stage II**	**Stage III**
	Serum beta-2 microglobulin < 3,5 mg/l; Serum albumin ≥3,5 g/dl	Neither stage I nor III	Serum beta-2 microglobulin > 5,5 mg/l

Table 2 Classification according to Durie and Salmon[8] and International Staging System[10]

	No. of participating centres	**No. of patients analysed**
Treatment survey 2004	59	500
Treatment survey 2006	66	503
Treatment survey 2008	35	386

Table 3 Number of participating centres and patients in the three treatment surveys

	Proportion of patients receiving therapy (patients not scheduled for HD-CT)						
Line of therapy/Year	Melphalan based [1]	VAD-like	Bendamustin based	Bortezomib-based	Lenalidomide-based	Thalidomide-based	Dexamethason mono
First line							
2006	49%	24%	7%	3%	0	3%	5%
2008	23%	30%	9%	14%	4%	9%	5%
Second line							
2006	27%	18%	10%	30%	0%	12%	1%
2008	20%	10%	14%	39%	6%	3%	3%
Third line							
2006	13%	6%	16%	35%	0%	15%	4%
2008	5%	3%	17%	42%	22%	6%	0%

Table 4 Distribution of different treatment schedules in 2006 and 2008

[1] Melphalan monotherapy or in combination with steroids

Figure 1 Primary treatment of multiple myeloma by stage. Pooled analysis (2006 and 2008).

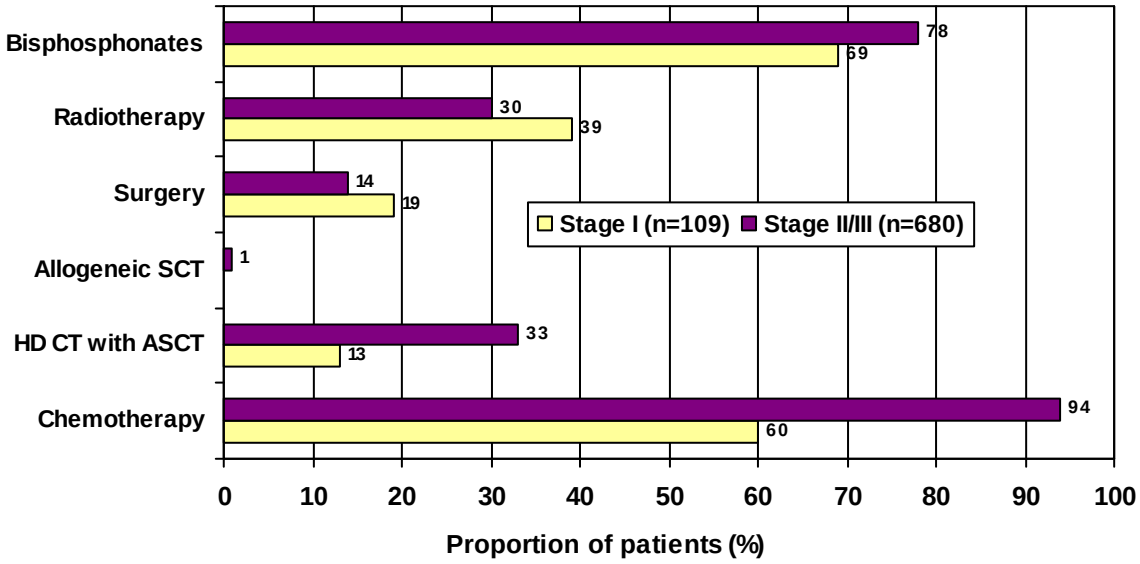


Figure 2 Proportion of patients receiving novel agents in first to 3rd line in 2004, 2006 and 2008

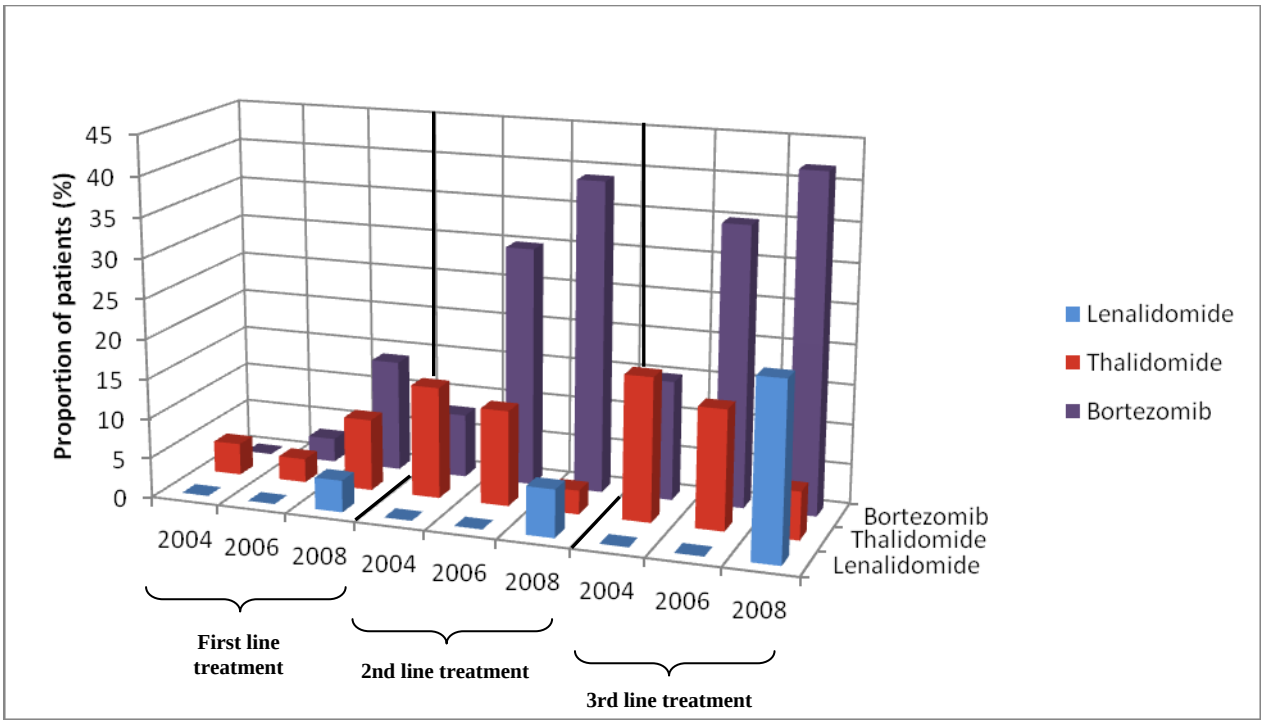


Figure 3 Treatment choice in first line by institution (n=204 patients)

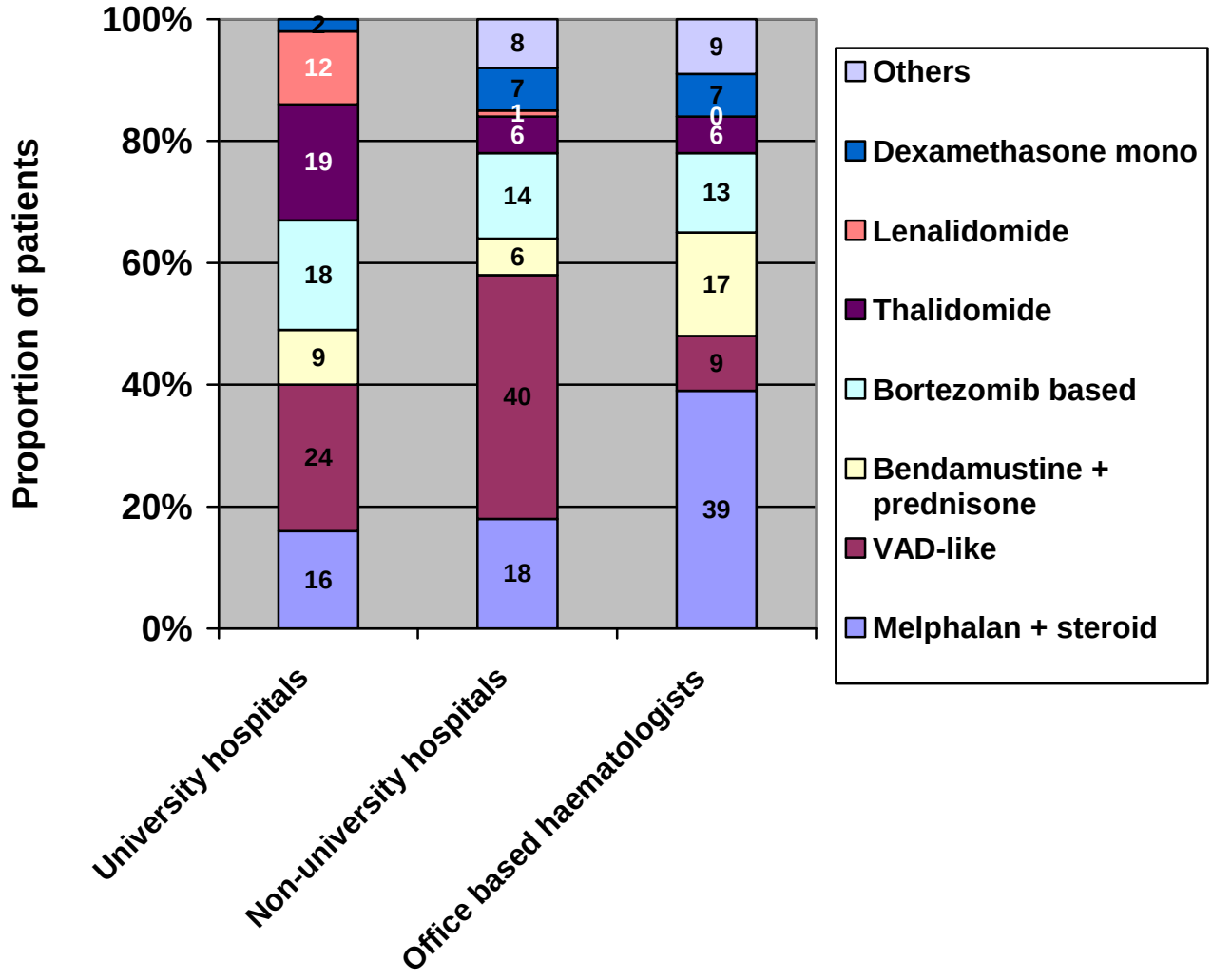
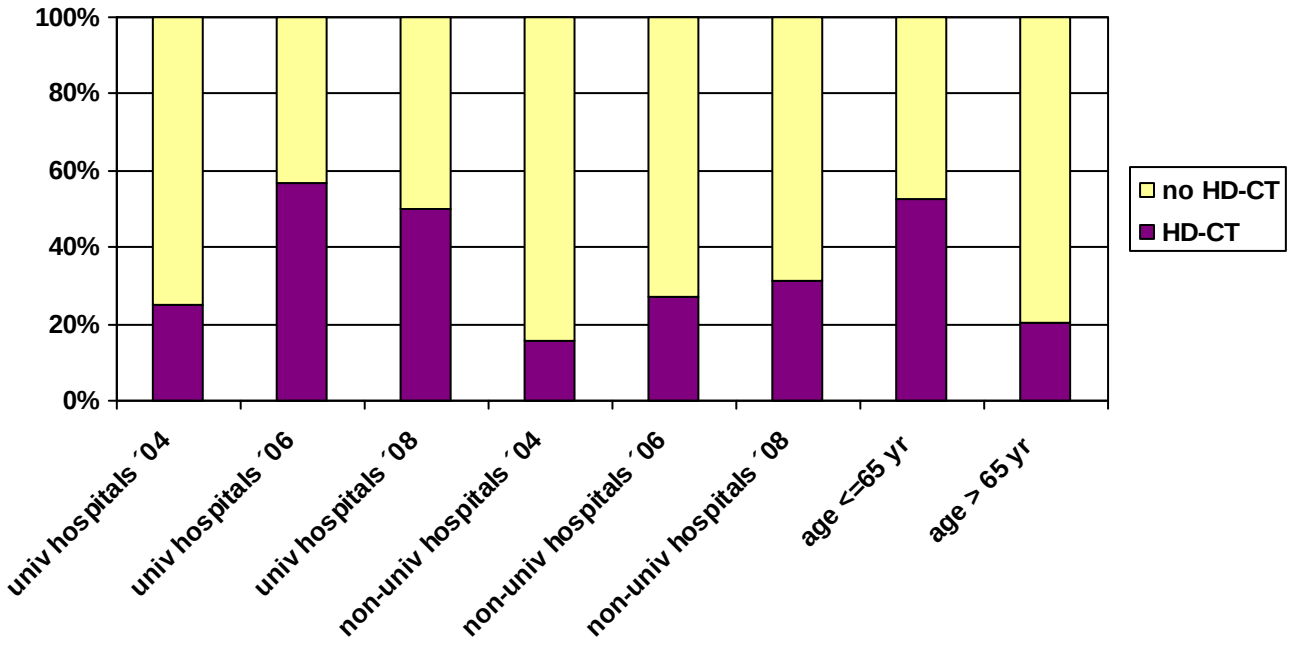


Figure 4 Proportion of patients receiving high dose chemotherapy in first-line by institution (2004-2008) and age (pooled analysis 2006 and 2008)



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