

Prognostic Factors in Elderly Patients with Multiple Myeloma Treated with Weekly Bortezomib

Anne-Laure Couderc^{1*}, Bertrand Coutanceau², Roger Mouawad², Bénédicte Mugnier¹, Amale Chebib², Elodie Baudry², Juliette Spinelli², Liliana Battaglia² and Pascal Chaibi²

¹Hospitals Assistance of Marseille, Marseille, France

²Hospitals Assistance of Paris, Paris, France

Abstract

Introduction and objectives: The incidence of multiple myeloma (MM) increases with age. There is a clear decrease in overall survival (OS) in older patients. The purpose of this study was to investigate prognostic factors of MM in this population.

Materials and methods: This is an analytic prospective single-center study conducted over 27 months including MM elderly patients treated with weekly subcutaneous bortezomib alone or associated with another chemotherapy.

Results: Our work has included 45 patients (median age 84.3 years). Most of them (77.7%) had a PS ≥ 2 , 75.6% were undernourished and 57, 1% had a Mini Mental State Examination (MMSE) < 26 . Haematological grade 3 toxicities were observed in 11% of patients. After 17 months mean follow-up, the median of OS was 18.6 months. In univariate analysis, significant predictors for OS were instrumental activities of daily living (IADL) ≥ 2 ($p = 0.003$), activities of daily living (ADL) < 5 ($p = 0.005$), the body mass index (BMI) < 21 ($p = 0.03$) and using hospitalization at home unit for bortezomib injections ($p = 0.01$). In multivariate analysis, significant predictors for OS were ADL < 5 ($p = 0.005$), using hospitalization at home unit ($p = 0.007$) and IADL ≥ 2 ($p = 0.05$).

Conclusion: In our work, weekly subcutaneous bortezomib was well tolerated. We have shown that functional decline, malnutrition and hospitalization at home unit are predictors of OS. These results lead us to reflect on the need to include these factors in the choice of treatment in elderly patients with MM.

Keywords: Multiple myeloma; Elderly patients; Weekly bortezomib; Prognostic factors

Introduction

Multiple myeloma (MM) is the second most common blood disease after lymphomas and represents 12% of hematological malignancies. Median age at diagnosis is 72 years, with 26% of the patients between 65 and 74 years old and 37% over 75 years [1].

Regarding the characteristics of the MM in elderly patients, no significant differences in clinical and biological MM presentation according to age has been described in the literature [2,3]. The incidence of the translocation (4:14), associated with poor prognosis in MM, appears to decrease with age, while the frequency of the deletion del (17) remains stable according to the study of the French-speaking Myeloma Intergroup [4]. However there is a clear decrease in overall survival (OS) of older patients with MM [5]. Numerous factors are involved in OS, especially in elderly patients. They decrease the feasibility of treatments such as comorbidities, performance status (PS) or renal failure [1,3]. The treatment abstention or insufficient specific treatment can also worsened the MM prognosis in elderly patients [3].

Bortezomib is a proteasome inhibitor used in the MM. The phase 3 VISTA trial demonstrated in older patients, bortezomib with melphalan-prednisone (MPV) best results in terms of complete response (CR), longer median time to progression and OS compared to melphalan-prednisone (MP) [6]. Nevertheless MPV was associated with more frequent serious adverse events including grade 3-4 digestive toxicities (20% versus 6%) and grade 3-4 neurological peripheral toxicities (13%). In order to reduce peripheral neuropathies, subcutaneous bortezomib was given instead of intravenous administration with comparable efficacy without significant differences between intravenous and subcutaneous administration of bortezomib concerning time to progression (10.4 vs 9.4 months) and one-year overall survival (72.6%

vs. 76.7%) [7]. Finally, the weekly administration of bortezomib reduces incidence of neurological toxicities with a comparable effectiveness to the protocol of the VISTA study, particularly in patients over 65 years [8,9] and can be proposed to frail elderly patients with adapted doses [10].

Our study was aimed to investigate prognostic factors in older patients with MM treated with weekly bortezomib alone or associated with another chemotherapy.

Materials and Methods

This is an analytic prospective single-center study conducted over 27 months (April 2013- July 2015) in the Charles Foix Hospital Onco-Hematology-Geriatric Unit in Ivry-Sur-Seine, France, including stage 3 MM elderly patients (Salmon and Durie Classification) treated with weekly subcutaneous bortezomib alone or associated with another chemotherapy. The bortezomib doses were 1.3 mg/m² according to the diagram Day (D) 1, D4, D8, D11, D 22 for the first stage and weekly from second cycle. The bortezomib doses were adapted to the platelet count according to the recommendations of the laboratory and to plan: 1.3 mg / m² if platelets $> 150,000$ / mm³, 1 mg / m² if 100,000 to 150,000 platelets / mm³, 0.7 mg / m² if between 50,000 and 100,000 platelets / mm³, and no injection if platelets $< 50,000$ / mm³.

***Corresponding author:** Anne-Laure Couderc, Hospitals Assistance of Marseille, Marseille, France, Tel: 04 91 38 32 60; E-mail: anne-laure.couderc@ap-hm.fr

Received February 26, 2016; **Accepted** April 04, 2016; **Published** April 11, 2016

Citation: Couderc AL, Coutanceau B, Mouawad R, Mugnier B, Chebib A, et al. (2016) Prognostic Factors in Elderly Patients with Multiple Myeloma Treated with Weekly Bortezomib. J Integr Oncol 5: 162. doi:10.4172/2329-6771.1000162

Copyright: © 2016 Couderc AL, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

For each patient, age, sex, comorbidities with Charlson score related to age [11] and the Cumulative Illness Rating Scale [12], the number of drugs, the way of life, if the patient is isolated or lives alone, if hospitalization in care and rehabilitation unit for the cures and if hospitalization at home unit has been requested for bortezomib injections, the PS, the Mini Mental State Examination (MMSE) [13], the body mass index (BMI), existence of undernutrition and stage [14], activities of daily living (ADL) [15], instrumental activities of daily living (IADL) [16] were analyzed.

Laboratory tests considered were hemoglobin (Hb), leukocytes, neutrophils, platelets and the calculation of creatinine clearance using the Cockcroft and Gault formula, albumin, calcium levels, immunoglobulin (electrophoresis of proteins) and light chain levels and lytic bone lesions.

Our work has sought the treatment with bortezomib start date, if chemotherapy and/or radiotherapy were associated, adverse events of chemotherapy, toxicities grades and the treatment stop date.

The statistical study was realized with statistical software STATA 13.1. The results of quantitative variables were expressed as median and standard deviation. Follow up time was calculated as the interval between the date of diagnosis and last follow-up or death. For OS, defined as the time from the entry into the study and death, we used Kruskal-Wallis test (median comparison test); uni- and multivariate analysis for prognostic factors, hazard ratios and confidence intervals were calculated with a Cox regression model. For these tests, $p < 0.05$ was considered to be statistically significant.

Results

Patients and paraclinical characteristics

Patients and paraclinical characteristics are summarized in Table 1.

The population included 45 patients with stage 3 MM in the Onco-Hematology-Geriatric department of Charles Foix Hospital, in France. The median age was 84.3 ± 5.9 years (64-97 years) and 71.1% were female.

Most patients were living at home (95.6%), 31.1% were in isolation, 44.4% were hospitalized in care and rehabilitation unit and 64.4% used the hospitalization at home unit for bortezomib administration.

Patients treated with hospitalization at home unit were significantly less malnourished than other patients ($p = 0.004$), were more independent for activities of daily living ($p = 0.01$) and had better PS ($p = 0.03$).

Treatment and adverse events

Bortezomib was used in first line in 66.6% of patients, in second line in 20% of patients and 13.3% in third line. Bortezomib was associated with melphalan- prednisone (MP) in 13.3% of the patients and with monthly intravenous cyclophosphamide in 17.8% of the patients. Radiotherapy was used in 15.5% of patients.

Haematological toxicities were observed in 40% (thrombocytopenia 61.1%) with 11% grade 3 toxicities. Neurological grade 2 toxicities were noted in 4.4% and gastrointestinal toxicities $\leq$ grade 2 in 8.9%. Cardiovascular grade 3 toxicities were observed in 6.7% and 6.6% had a grade 3 infectious syndrome.

At the end of the study, 8 patients with persistent partial remission continue to receive bortezomib treatment.

	Number of Evaluated Patients	Number of Patients	%	Median
Age (years)				84.3 ± 5.9
Sex				
Women	45	32	71.1	
Men		13	28.9	
Cardiovascular comorbidities	45	34	75.6	
Type 2 diabetes	45	5	11.1	
History of cancer or blood disease	45	8	17.8	
Number of drugs ≥ 5	45	27	60	5.6 ± 3.5
Charlson aa				
> 7	45	23	51.1	7.8 ± 1.6
≤ 7		22	48.9	
CIRS-G				
> 6	45	24	53.3	7.3 ± 2.4
≤ 6		21	46.7	
ADL				
< 5	45	17	37.8	4.8 ± 1.2
≥ 5		28	62.2	
IADL				
≥ 2	45	21	46.7	1.7 ± 1.6
< 2		24	53.3	
MMSE				
< 26	35	20	57.1	22.6 ± 6.4
≥ 26		15	42.9	
PS				
1	45	10	22.2	2.1 ± 0.8
2		19	42.2	
3		15	33.3	
4		1	2.2	
BMI				
< 21	45	18	40	23.4 ± 5.4
≥ 21		27	60	
Anemia (Hb < 12 g/dl)	45	38	84.4	10.2 ± 1.7 g/dl
Thrombopenia (platelets $< 150000/\text{mm}^3$)	45	13	28.9	$211\ 822 \pm 102\ 213/\text{mm}^3$
Neutropenia (neutrophils $< 1500/\text{mm}^3$)	45	4	8.9	$3842.4 \pm 2995.1/\text{mm}^3$
Hypercalcemia (calcémie $> 2,55$ mmol/l)	45	10	22.2	$2,44 \pm 1,46$ mmol/l
Renal failure (clairance < 60 ml/min)	45	33	73.3	61.3 ± 32.9 ml/min
Albumin (g/l)				
> 35 g/l	43	10	23.3	$30,9 \pm 6,7$ g/l
≤ 35 g/l		33	76.7	
Lytic bone lesions	45	30	66,7	
Myeloma type				
IgG	45	24	53.3	
IgA		14	31.1	
IgM		0	0	
IgD		0	0	
Light chain		7	15.6	
Bortezomib				
First line	45	30	66,6	
2 nd line		9	20	
3 rd line		6	13,3	

Table 1: Patients and paraclinical characteristics.

Predictive factors for overall survival

At the time of analysis, after a median follow-up period 17 months,(7.5- 27 months), 20 patients died (44.4%) including 12 deaths due to MM, 1 secondary to chemotherapy toxicity, 6 due to comorbidities and 1 from unknown reason. The median OS was 18.6 months (Figure 1) and the median progression-free survival (PFS) was 17.1 months.

In univariate analysis, significant predictive factors for OS were IADL ≥ 2 ($p=0,003$), ADL<5 ($p=0,005$), BMI<21 ($p=0,03$), hospitalization at home unit ($p=0,01$), hypercalcemia ($p=0,05$) and a serum albumin level<25 g/l ($p=0,05$). Severe chronic renal failure was marginally associated with OS ($p = 0.09$).

Multivariate analysis of risk was performed using the Cox proportional hazard regression analysis adjusted for ADL, IADL and hospitalization at home unit, we identified that only ADL, hospitalization at home unit steel a very good predictive factors and in a lower IADL. The results are summarized in Table 2.

Predictive factors for toxicity

No predictive geriatric factor for hematologic toxicity and non-hematological toxicity was found significantly in our study.

Discussion

Age is a poor prognosis factor in MM resulting in a clear decrease in OS [17]. A meta-analysis of 1435 MM patients over 65 years old showed the negative impact of age on the OS and grade 3-4 non-hematological toxicities [18]. In another study in MM patients treated with bortezomib, the population over 75 years old had an OS lower than younger patients (32,9 vs. 50,7 months) [19]. In our study, the median OS for older patients was 18,6 months with a 17 months average follow-up and 55,6% of patients were still alive at the end of the study. In the VISTA trial comparing patients receiving VMP v_s MP, 344 VMP treated patients with a mean age lower than our study (71 years) and a 36, 7 months median follow-up, the death rate was 32%. Our study presented a greater death rate with an older (median age of 84, 3 years) and frailer population. The lower median OS in our study was also explained by MM severity (stage 3 MM) and 33% of patients were treated in second and third line with bortezomib.

The elderly population is relatively heterogeneous and so, geriatric factors and frailties will be heavily important to assess the prognosis of MM. Comorbidities are associated with a median survival reduction

Prognostic factors	Univariate		Multivariate	
	Hazard ratio (95% CI)	p	Hazard ratio (95% CI)	p
IADL ≥ 2	3.06 (0.92-10.25)	0.003	0.08 (0.006-1)	0.05
ADL < 5	0.08 (0.017-0.37)	0.005	0.01 (0.0004-0.2)	0.005
BMI < 21	0.24 (0.07-0.79)	0.03		
Hypercalcemia	2.35 (0.68-8.09)	0.05		
Albumin < 25 g/l	0.23 (0.07-0.811)	0.05		
Severe renal failure	0.89 (0.79-0.99)	0.09		
Hospitalization at home unit	0.074 (0.016-0.34)	0.01	0.03 (0.002-0.3)	0.007

Table 2: OS prognostic factors in uni-and multivariate analysis.

in MM [1]. Offidani et al. used the Charlson score to create a score of survival in MM [20]; Palumbo et al. presented a mortality risk and non-haematological toxicity score in MM including the Charlson score [21]. In our study, patients were vulnerable: 75, 6% of them were suffering from cardiovascular comorbidities and their average comorbidity scores were relatively high (7, 8 for Charlson aa and 7, 3 for CIRS-G). Comorbidities were not significantly associated with OS in our study due to wide variety of associated diseases in patients.

Nearly half of patients had a loss of autonomy in the study; 46, 7% of patients had a IADL ≥ 2 and 37, 8% had a ADL<5. In uni-and multivariate analysis, we demonstrated that ADL and IADL were significantly related to the risk of death (respectively $p = 0,005$ and $p = 0,05$). These results corroborate with the study of Palumbo et al. [21] in which activities of daily living were prognostic factors for OS and non-haematological toxicities. Functional status is associated with OS in most studies on solid tumors in elderly [22,23] and is an important mortality predictor in geriatric oncology.

The malnutrition prevalence in elderly cancer patients is important [24]. It causes more infections, poorer survival and increases the hospitalization duration. In our study, we have shown for the first time in patients with MM, that BMI<21 ($p = 0,03$) is a prognostic factor for OS. Other studies [23,25,26] conducted in elderly patients suffering from solid tumors and hematological malignancies have shown the malnutrition negative impact on survival. Among 348 patients over 70 years suffering from various cancers and receiving chemotherapy, malnutrition detected with Mini Nutritional Assessment (MNA) [27] was a risk factor for early mortality at 6 months [25]. In a study in elderly patients with large B cell lymphoma treated with reduced doses of R-CHOP [28], hypoalbuminemia was a risk factor for poorer survival. In our study, we found that an albumin level<25 g/l was significantly ($p = 0,05$) related to mortality. In literature, no other study has shown the impact of malnutrition and severe malnutrition on OS in MM patients.

Hypercalcemia ($p = 0,05$) and severe renal failure ($p=0,09$) were associated with poorer survival in our study. The prevalence of renal failure in the development of MM is 30-50% and in older population, an another risk of renal failure due to comorbidities (in particular cardiovascular comorbidities) is important. However, according to the literature, renal failure is associated with higher morbidity and mortality in MM [29]. The used treatment should be tailored to the creatinine clearance and the choice of chemotherapy in elderly patients should consider renal failure. Bortezomib can be used in renal failure [10,29] without dose adjustment unlike other MM treatments as lenalidomide.

Another survival factor in our study was the use of hospitalization

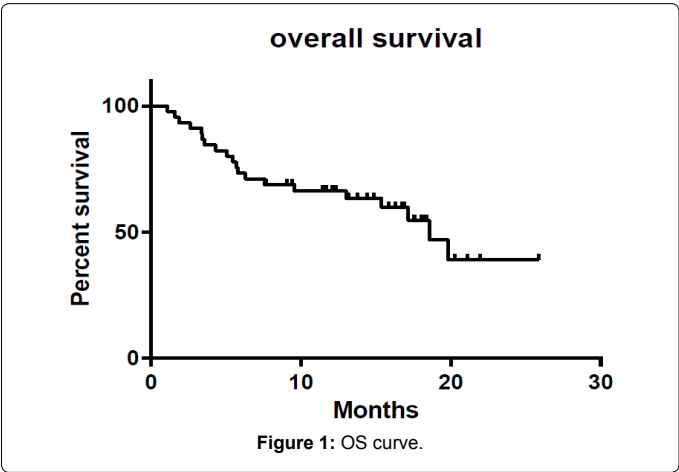


Figure 1: OS curve.

at home unit to perform the weekly bortezomib injections. Patients who could benefit from this organization 3 weeks/4 with an injection monthly realized in traditional hospitalization were more independent ($p = 0,01$), less malnourished ($p = 0,004$) and with better PS ($p = 0,03$). The use of hospitalization at home unit is therefore a real challenge for the future, to support and treat patients in their place to live and thus to improve their quality of life.

Our population has been treated with weekly bortezomib alone (68,9%) or associated with another chemotherapy (MP in 13,3% of cases and monthly intravenous cyclophosphamide in 17,8%). The low rate of grade 3-4 cytopenia (11%) compared to literature is related to the fact that bortezomib was often used alone and weekly. In Moreau et al. study [7], 57% of patients receiving subcutaneous bortezomib in a dose of 1,3 mg/m² according to the diagram D1 D4 D8 D11 every 21 days, experienced grade 3 hematologic toxicity in 13% of patients. In our study, the used bortezomib dose was 1, 3 mg/m² adapted tailored to the platelet; the injections protocol was D1,D4, D8, D11 and D22 for the first cycle and then weekly on other cycles. Hematological grade 3 toxicity was 11% according to studies in literature.

Neuropathy grade ≥ 2 toxicity was 24% in Moreau et al. study and 4.4% in our study. The low rate of neuropathy in our patients was due to subcutaneous and weekly administration. In the study of Brinthen et al. [30], grade 3-4 neuropathy rate was only 8% when bortezomib was administrated weekly and intravenously.

The European Working Group on the Myeloma proposed a regimen for elderly patients with MM [1,31] that we used in our study (1,3 mg/m² every week) from the second cycle. But dose reduction was tailored to the platelets number in our work and not to age, frailty and comorbidities as proposed by Palumbo et al. [1]. A study with a greater number of older patients with MM treated with bortezomib and with a longer follow-up should be conducted to determine the effectiveness and tolerance of this chemotherapy and to identify other risk factors of toxicity and mortality.

Conclusion

Age is a factor of poor prognosis in MM but the older population is heterogeneous. In the same age group patients, significant differences considering the physical, cognitive, functional and/or social characteristics are present. Our study showed that, the CGA impact (dependence in activities of daily living, instrumental activities of daily living and malnutrition) OS of elderly MM patients treated with weekly subcutaneous bortezomib. Hospitalization at home unit for autonomous elderly patients and/or in good condition is also a real challenge to improve the quality of life and survival. A study on a larger number of elderly patients would be particularly interesting to know the impact of outpatient care in this population.

References

- Palumbo A, Brinthen S, Ludwig H, Dimopoulos MA, Bladé J, et al. (2011) Personalized therapy in multiple myeloma according to patient age and vulnerability: a report of the European Myeloma Network (EMN). *Blood* 118: 4519-4529.
- Bladé J, Muñoz M, Fontanillas M, San Miguel J, Alcalá A, et al. (1996) Treatment of multiple myeloma in elderly people: long-term results in 178 patients. *Age Ageing* 25: 357-361.
- Rodon P, Linassier C, Gauvain JB, Benboubker L, Goupille P, et al. (2001) Multiple myeloma in elderly patients: presenting features and outcome. *Eur J Haematol* 66: 11-17.
- Avet-Loiseau H, Hulin C, Campion L, Rodon P, Marit G, et al. (2013) Chromosomal abnormalities are major prognostic factors in elderly patients

- with multiple myeloma : the intergroupe francophone du myelome experience. *J Clin Oncol* 31: 2806-2809.
- Harousseau JL (2010) Multiple myeloma in the elderly: when to treat, when to go to transplant. *Oncology (Williston Park)* 24: 992-998.
- Mateos MV, Richardson PG, Schlag R, Khuageva NK, Dimopoulos MA, et al. (2010) Bortezomib plus melphalan and prednisone compared with melphalan and prednisone in previously untreated multiple myeloma: updated follow-up and impact of subsequent therapy in the phase III VISTA trial. *J Clin Oncol* 28: 2259-2266.
- Moreau P, Pylypenko H, Grosicki S, Karamanesht I, Leleu X, et al. (2011) Subcutaneous versus intravenous administration of bortezomib in patients with relapsed multiple myeloma: a randomized, phase 3, non-inferiority study. *Lancet Oncol* 12: 431-440.
- Mateos MV, Oriol A, Martinez-Lopez J, Gutiérrez N, Teruel AI, et al. (2010) Bortezomib, melphalan and prednisone versus bortezomib, thalidomide, and prednisone as induction therapy followed by maintenance treatment with bortezomib and thalidomide versus bortezomib and prednisone in elderly patients with untreated multiple myeloma : a randomized trial. *Lancet Oncol* 11: 934-941.
- Palumbo A, Brinthen S, Rossi D, Cavalli M, Larocca A, et al. (2010) Bortezomib-melphalan-prednisone-thalidomide followed by maintenance with bortezomib-thalidomide compared with bortezomib-melphalan-prednisone for initial treatment of multiple myeloma: a randomized controlled trial. *J Clin Oncol* 28: 5101-5109.
- Palumbo A, Rajkumar SV, San Miguel JF, Larocca A, Niesvizky R, et al. (2014) International Myeloma Working Group consensus statement for the management, treatment, and supportive care of patients with myeloma not eligible for standard autologous stem-cell transplantation. *J Clin Oncol* 32: 587-600.
- Charlson ME, Pompei P, Ales KL, MacKenzie CR (1987) A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 40: 373-383.
- Miller MD, Paradis CF, Houck PR, Mazumdar S, Stack JA, et al. (1992) Rating chronic medical illness burden in geropsychiatric practice and research: application of the Cumulative Illness Rating Scale. *Psychiatry Res* 41: 237-248.
- Folstein MF, Folstein SE, McHugh PR (1975) "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 12: 189-198.
- www.has-sante.fr
- Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW (1963) studies of illness in the aged. the index of adl: a standardized measure of biological and psychosocial function. *jama* 185: 914-919.
- Lawton MP, Brody EM (1969) Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist* 9: 179-186.
- Ludwig H, Bolejack V, Crowley J, Bladé J, Miguel JS, et al. (2010) Survival and years of life lost in different age cohorts of patients with multiple myeloma. *J Clin Oncol* 28: 1599-1605.
- Brinthen S, Mateos MV, Zweegman S, Larocca A, Falcone AP, et al. (2013) Age and organ damage correlate with poor survival in myeloma patients: meta-analysis of 1435 individual patient data from 4 randomized trials. *Haematologica* 98: 980-987.
- San Miguel JF, Schlag R, Khuageva NK, Dimopoulos MA, Shpilberg O, et al. (2013) Persistent overall survival benefit and no increased risk of second malignancies with bortezomib-melphalan-prednisone versus melphalan-prednisone in patients with previously untreated multiple myeloma. *J Clin Oncol* 31: 448-455.
- Offidani M, Corvatta L, Polloni C, Centurioni R, Visani G, et al. (2012) Assessment of vulnerability measures and their effect on survival in a real-life population of multiple myeloma patients registered at Marche Region Multiple Myeloma Registry. *Clin Lymphoma Myeloma Leuk* 12: 423-432.
- Palumbo A, Brinthen S, Mateos MV, Larocca A, Facon T, et al. (2015) Geriatric assessment predicts survival and toxicities in elderly myeloma patients: an International Myeloma Working Group report. *Blood* 125: 2068-2074.
- Girones R, Torregrosa D, Maestu I, Gómez-Codinac J, Jose M, et al. (2012) Comprehensive geriatric assessment (CGA) of elderly lung cancer patients: A single-center experience. *J Geriatr Oncol* 3: 98-103.

23. Kanesvaran R, Li H, Koo KN, Poon D (2011) Analysis of prognostic factors of comprehensive geriatric assessment and development of a clinical scoring system in elderly Asian patients with cancer. *J Clin Oncol* 29: 3620-3627.
24. Retornaz F, Seux V, Sourial N, Braud AC, Monette J, et al. (2007) Comparison of health and functional status between elderly inpatients with and without cancer admitted to a geriatric internal medicine unit. *J Gerontol Med Sci* 62: 917-922.
25. Soubeyran P, Fonck M, Blanc-Bisson C, Blanc JF, Ceccaldi J, et al. (2012) Predictors of early death risk in older patients treated with first-line chemotherapy for cancer. *J Clin Oncol* 30: 1829-1834.
26. Aaldriks AA, Giltay EJ, le Cessie S, van der Geest LG, Portielje JE, et al. (2013) Prognostic value of geriatric assessment in older patients with advanced breast cancer receiving chemotherapy. *Breast* 22: 753-760.
27. Guigoz Y, Vellas B, Garry PJ, Nourhashemi F, Bennahum D, et al. (1994) Mini Nutritional Assessment : A practical assessment for grading the nutritional state of elderly patients. *Facts and Research in Gerontology*, NestlÃ© Ltd/Clintec, supp. 2.
28. Peyrade F, Jardin F, Thieblemont C, Thyss A, Emile JF, et al. (2011) Attenuated immunochemotherapy regimen (R-miniCHOP) in elderly patients older than 80 years with diffuse large B-cell lymphoma: a multicentre, single-arm, phase 2 trial. *Lancet Oncol* 12: 460-468.
29. Dimopoulos MA, Terpos E, Chanan-Khan A, Leung N, Ludwig H, et al. (2010) Renal impairment in patients with multiple myeloma: a consensus statement on behalf of the International Myeloma Working Group. *J Clin Oncol* 28: 4976-4984.
30. Bringhen S, Larocca A, Rossi D, Cavalli M, Genuardi M, et al. (2010) Efficacy and safety of once-weekly bortezomib in multiple myeloma patients. *Blood* 116: 4745-4753.
31. Wildes TM, Rosko A, Tuchman SA (2014) Multiple myeloma in the older adult: better prospects, more challenges. *J Clin Oncol* 32: 2531-2540.