Poorer Survival in Multiple Myeloma Correlates with Patients' age and is Linked to a Higher Stage at Presentation but Prognostic Parameters Reflecting the Biology of the Myeloma Clone are not Associated with Age.

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Abstract

Up to now no systematic analysis on the impact of different age categories on survival in patients with multiple myeloma has been reported. Information on possible correlations of host and tumor related prognostic factors with different age categories are lacking. We studied these parameters in a large cohort of patients with multiple myeloma (n=10.750) submitted by participating institutions and groups in the international staging system (ISS) project. Prognostic factors were recorded and age was calculated at start of initial chemotherapy. Patients were grouped into 6 age cohorts (<40, 40-<50, 50-<60, 60-<70, 70-<80 and ≥80 years). P values were calculated with the Jonckheere-Terpstra test and Spearman's correlation coefficient was used where appropriate.

The sequential median survivals constantly decreased by decade from 61 months to 60, 53, 40, 32 and 24 months in the 6 patient cohorts from age < 40 years to age >80 years examined, respectively, with a median value of 44 months (p<0.0001). The distribution of prognostic factors by age revealed a highly significant correlation between high serum $ß_2$ microglobulin ($Sß_2M$, ≥3.5mg/dl) and age, ranging from 45% in patients in the youngest to 75% of patients in the oldest age cohort (r=0.17 (0.15-0.19), p<0.0001). A similar correlation was seen between low serum albumin (<3.5g/dl) and age: The proportion of patients with low serum albumin levels increased from 32% in patients at age < 40 years to 54% in patients > 80 years (r=-0.11(-0.13,-0.09), p<0.0001). Consequently, as $Sß_2M$ and serum albumin constitute the prognostic parameters of the ISS, a close correlation between ISS stage and age was found (p< 0.0001). The proportion of patients with ISS stage I ($Sß_2M$ < 3.5mg/dl and serum albumin ≥ 3.5 mg/dL) was 40% in patients aged <40 years and only 12% in those aged ≥80 years. In contrast, 44% of patients of the oldest and 31% of the youngest age cohort presented with ISS stage III. In addition, a similar, albeit lesser trend was noted for decreasing hemoglobin with age (r= -0.08 (-0.10,-0.07, p<0.0001) and increasing serum creatinine with age (r=0.08 (0.06, 0.10), p <0.0001).

The parameters reflecting the biology of the myeloma clone did not vary between different ages cohorts. Bone marrow plasma cell infiltration (BMPC) ≥33%, CRP levels >=0.8 (mg/dL) and normal LDH was seen in similar frequencies in the different age categories. Similarly, no age dependent variation in cytogenetically defined prognostic variables was seen. The proportion of patients with Del 13 and of those with t (11; 14), t (4; 14) did not differ between the different age categories (these data were obtained in a limited number of patients only (616, 544 and 418 patients, respectively)).

In conclusion, age was identified as important prognostic factor in the six different age cohorts examined. Poorer survival with higher age is closely linked to higher ISS stage. In addition, creatinine and low haemoglobin correlate, albeit to a lesser degree, with increasing age, but not parameters reflecting adverse biologic features of the tumor clone (LDH, BMPC, CRP, del 13, t(11;14) t(4;14). Hence, an ailing host and not a more aggressive tumor clone seems to account for the inverse correlation between survival and age.

Introduction and Objectives

Up to now no systematic analysis on the impact of different age categories on survival in patients with multiple myeloma has been reported. Information on possible correlations of host and tumor related prognostic factors with different age categories are lacking.

We therefore aimed to investigate possible interrelations between age, various prognostic factors and survival in 10.750 patients with multiple myeloma (MM).

Methods

We studied various prognostic parameters in a large cohort of patients with MM (n=10.750) submitted by participating institutions and groups in the international staging system (ISS) project. Prognostic factors were recorded and age was calculated at start of initial chemotherapy. Patients were grouped into 6 age cohorts (<40, 40-<50, 50-<60, 60-<70, 70-<80 and ≥80 years). P values were calculated with the Jonckheere-Terpstra test and Spearman's correlation coefficient was used where appropriate.

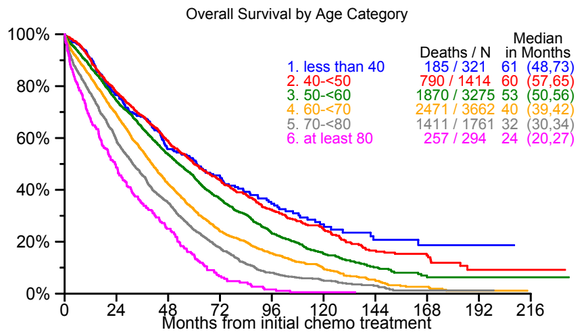
Results

Table 1 shows age at start of initial chemotherapy of the entire patient population treated in Asia, Europe and North America.

Variable	Statistic	Asia	Europe	North America
Age (Years)	N Mean (Std) Median	983 65.6 (10.2) 66.0	6245 58.0 (9.9) 58.0	3499 62.0 (11.0) 63

Std- standard deviation

Figure 1 shows overall survival by age categories.



The sequential median survivals constantly decreased by decade from 61 months to 60, 53, 40, 32 and 24 months in the 6 patient cohorts from age < 40 years to age >80 years examined, respectively, with a median value of 44 months (p<0.0001).

Comparison of survival by gender and race revealed similar outcome in patients with both gender but shorter survival in blacks.

Table 2 shows the distribution of prognostic factors by age category.

Factor	< 40	40-<50	50-<60	60-<70	70-<80	at least 80
B2M>=3.5 (mcg/mL)	45%	45%	52%	60%	68%	75%
Albumin<3.5 (g/dL)	32%	34%	38%	41%	46%	54%
HGB<10 (g/dL)	39%	37%	38%	41%	43%	50%
Creatinine>=2 (mg/dL)	18%	14%	16%	17%	20%	21%
PLT<130 (x10^3/uL)	14%	10%	11%	13%	12%	14%
Calcium>=10 (mg/dL)	34%	33%	35%	34%	32%	30%
CRP>=0.8 (mg/dL)	23%	26%	29%	31%	29%	30%
BMPC>=33%	59%	58%	58%	60%	60%	58%
ISS Stage I II III	40% 28% 31%	38% 36% 26%	32% 38% 30%	25% 40% 35%	20% 41% 39%	12% 44% 44%
n/N (%): n- Number with Factor for Group Level, N- Number Evaluable						

The distribution of prognostic factors by age revealed:

1) a highly significant correlation between high serum $ß_2$ microglobulin (≥3.5mg/dl) and age, ranging from 45% in patients in the youngest to 75% of patients in the oldest age cohort (r=0.17 (0.15-0.19), p<0.0001).

2) a similar correlation low serum albumin (<3.5g/dl) and age: The proportion of patients with low serum albumin levels increased from 32% in patients at age < 40 years to 54% in patients > 80 years (r=-0.11(-0.13,-0.09), p<0.0001).

3) a close correlation between ISS stage and age (p< 0.0001). The proportion of patients with ISS stage I ($Sß_2M$ < 3.5mg/dl and serum albumin ≥ 3.5 mg/dL) was 40% in patients aged <40 years and only 12% in those aged ≥80 years.

In contrast, 44% of patients of the oldest and 31% of the youngest age cohort presented with ISS stage III.

4) a similar, albeit lesser trend for decreasing hemoglobin with age (r= -0.08 (-0.10,-0.07, p<0.0001) and increasing serum creatinine with age (r=0.08 (0.06, 0.10), p <0.0001).

5) The parameters reflecting the biology of the myeloma clone did not vary between different age cohorts. Bone marrow plasma cell infiltration (BMPC) ≥33%, CRP levels >=0.8 (mg/dL) and normal LDH was seen in similar frequencies in the different age categories. Similarly, no age dependent variation in cytogenetically defined prognostic variables was seen.

The proportion of patients with Del 13 and of those with t (11; 14), t (4; 14) did not differ between the different age categories (these data were obtained in a limited number of patients only (616, 544 and 418 patients, respectively)).

Conclusions

Age was identified as important prognostic factor in the six different age cohorts examined. Poorer survival with higher age is closely linked to higher ISS stage. In addition, creatinine and low haemoglobin correlate, albeit to a lesser degree, with increasing age, but not other known risk factors such as those reflecting adverse biologic features of the tumor clone (LDH, BMPC, CRP, del 13, 1(11;14), t(4;14)

Participating Centers

Mayo Clinic and Eastern Oncology Collaborative Group (ECOG), Rochester, Minnesota, U.S.A.
Spanish Cooperative Groups: (GEM), University of Salamanca; (PETHEMA), Hospital Clinic, Barcelona; (PETHEMA), Hospital Universitario, Madrid, Spain
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NORDIC Myeloma Study Group: Malmö; Lund University Hospital, Lund, Sweden.