Treat or palliate: outcomes of very elderly myeloma patients

Limited data are available on outcomes of myeloma in patients over 85 years of age, an age group in which the incidence of myeloma peaks, as these patients are poorly represented in clinical trials. We report a retrospective analysis of treatment patterns and survival outcomes of very old (≥85 years) myeloma patients from a single cancer network in England, UK. Two-thirds of the patients received immunomodulatory drugs/proteasome inhibitors as their first-line treatment. Despite observed higher early mortality, improved relative survival rates in the very elderly suggests treatment should not be withheld based on advanced age at diagnosis.

Myeloma is a disease of the elderly. According to UK data[1] 45% of new diagnoses are recorded in people aged ≥75 years and myeloma incidence rates peak in the 85 -to 89-year old age group. Shifting population demographics have resulted in a doubling of the proportion of newly diagnosed cases above the age of 80.[2] Elderly patients are underrepresented in cancer clinical trials.[3-5] Novel agents (immunomodulatory drugs/proteasome inhibitors) as first-line and salvage treatments have benefited younger patients[6] and, as reported recently, transplant-ineligible patients;[7] however, patients >80 years old were not included in that analysis. No improvement in overall survival over the last two decades was observed in a cohort study of octogenarians.[8]

Data from the Greek myeloma group showed that patients who received novel agents fared better.[9] The median overall survival of an elderly (≥80 years) cohort of myeloma patients was 22 months, with an early mortality rate (at 2 months) of 14%.[9] Performance status and treatment with novel agents, in addition to stage, age and cytogenetics, were independent prognostic factors for survival.[8] Comorbidity burden and performance status were predictive of outcomes in a retrospective study from Japan of myeloma patients ≥80 years old.[10]

Treatment of elderly myeloma patients presents significant challenges.[11] Comprehensive geriatric assessment tools have been developed for use both in clinical trials and to inform decisions in everyday practice.[12] Key considerations when making therapy decisions for elderly patients include estimated survival, symptom burden, toxicity and impact on quality of life of both the disease and its treatment.[13]

We retrospectively analyzed outcomes of very elderly (≥85 years old), newly diagnosed myeloma patients eligible for therapy. The study was approved by the Institutional Review Board. Treatment data and survival status from January 2009 through October 2016 were retrieved from the electronic chemotherapy prescription database. Time for all survival outcomes was measured from the start of first-line therapy. Time to next treatment was measured until the earliest of either next-line treatment or death. Relative survival rates were calculated to examine the impact of the diagnosis of myeloma on overall survival. Expected survival was calculated with the conditional method from UK death rates obtained from the Office for National Statistics through the Human Mortality Database (*www.mortality.org*). Statistical analyses were done with Stata 11 (StataCorp, College Station, TX, USA) and EZR.[14]

During the studied period, 1,328 consecutive patients were treated for myeloma in the Thames Valley Network. Of these, 89 patients diagnosed at the age of ≥85 years were observed from the start of first-line treatment (*Online Supplementary Figure S1*) and had a median follow-up of 37 months. The median age of this group was 87 years (range, 85-96 years). Fifty-six percent were men. The gender distribution did not differ across age groups. On average 8.4% of all new myeloma patients starting treatment each year belonged to the very elderly group and there were no apparent time trends.

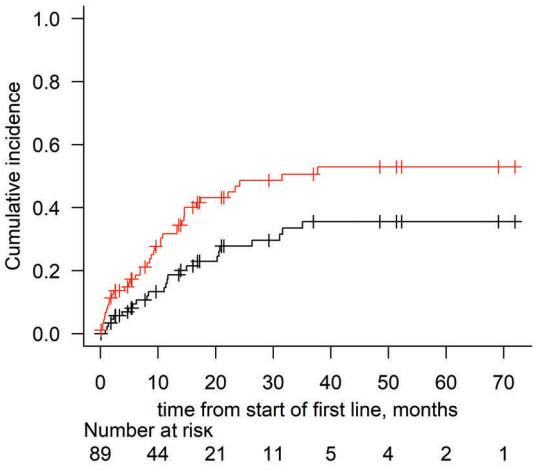

Figure 1. Cumulative incidence curves. Cumulative incidence curves of competing events of second-line treatment (black curve) and death before second-line treatment (red curve) in the ≥85-year old group.

First-line treatment was thalidomide-based (thalidomide and dexamethasone; cyclophosphamide, thalidomide and dexamethasone; melphalan, prednisolone and thalidomide) in 44 patients (49.4%), bortezomib-based (bortezomib and dexamethasone; bortezomib, cyclophosphosphamide and dexamethasone; melphalan, prednisone and bortezomib) in 14 (15.7%), alkylator-only (melphalan and prednisolone or cyclophosphamide and prednisolone) in 29 (32.6%) and lenalidomide-dexamethasone in two (2.2%). Twenty-six of 89 patients received second-line treatment (bortezomib-based in 14/26) and only nine reached third-line therapy (lenalidomide-dexamethasone in 6/9 patients). Only two out of 89 patients were enrolled in clinical trials for any line of treatment. On average, the very elderly patients received fewer lines of treatment until their death than younger patients, in keeping with their shorter overall survival (*Online Supplementary Figure S2*). The maximum cumulative incidence of second-line treatment was 35.5% [95% confidence interval (CI): 24.4-46.8%] (Figure 1), which was considerably lower than in younger groups (65.8% in 75- to 84-year olds, 78.9% in 65- to 74-year olds and 76.5% in those younger than 65; Gray test P=0.0007) (*Online Supplementary Figure S3*). The maximum cumulative incidence of death before second-line therapy was 52.9%. (95% CI: 40.4-64%) (Figure 1), which was much higher than in younger patients (24.6% in the 75- to 84-year old group, 13.6% in the 65- to 74-year old group and 7.4% in those <65 years old; Gray test, $P<10^{-4}$) (*Online Supplementary Figure S4*). Time to next treatment was shorter in the very old (median 11.7 months) than in younger patients (*Online Supplementary Figure S5*).

The median overall survival of the very elderly patients was 22.2 months, which was significantly shorter than that of younger groups (75- to 84-year olds: 30.3 months; 65- to 74-year olds: 63.6 months; <65 years: not

reached). No difference in survival between men and women was observed. The early mortality rate was significantly higher in the advanced age cohort: 11.3% at 2 months and 17.3% at 6 months. The comparative 6-month mortality rate was 10.1% in the 75- to 84-year old group, 5.9% in the 65- to 74-year old group and 6.7% in the <65-year olds (log-rank $P<10^{-4}$, *Online Supplementary Figure S6*).

The Charlson Comorbidity Index (CCI) score was available for 44/89 very elderly cases (49.4%). The median CCI score was 6 (range, 4-14; interquartile range, 5-6). CCI scores were not statistically different between patients who received first-line treatment regimen based only on an alkylator or immunomodulatory drug/proteasome inhibitor (Mann-Whitney, P=0.99). No impact of lower CCI scores (CCI ≤5) *versus* higher scores (CCI≥6) on overall survival could be detected (log-rank P=0.54).

The International Scoring System (ISS) score at diagnosis was available for a small number of patients. ISS 3 cases tended to have shorter overall survival and a non-significant association with higher CCI score was also noted (*data not shown*).

Patients who received alkylator-only regimens as first-line therapy had a significantly shorter overall survival than patients treated with immunomodulatory drugs/proteasome inhibitors (median 14 months *versus* 35 months, respectively; log-rank P=0.0003) (*Online Supplementary Figure S7A*). The median time to next treatment of very elderly patients treated first line with immunomodulatory drugs/proteasome inhibitors was 14.6 months compared to 6.9 months for patients who were treated first line with alkylator-only regimens (log-rank P=0.012) (*Online Supplementary Figure S7B*).

The relative survival of patients ≥85 years at 2 years after starting first-line treatment was 0.92 (range, 0.88-0.96) for male patients and 0.88 (range, 0.84-0.91) for female patients. In comparison, in the youngest age group (<65 years old) relative survival at 2 years after starting first-line treatment had already dropped to 0.7 (range, 0.67-0.73) for male and female patients and continued to drop after that (Figure 2).

In this retrospective study, we explored real-world treatment patterns and survival outcomes of myeloma patients at the highest end of the myeloma age distribution (>90th percentile) in the most recent therapeutic era. We believe that our cohort is representative of everyday practice as we included all consecutive patients treated in a defined region and period at several different sites. Our cohort is the oldest reported in the literature. The survival of these patients differs substantially from that of the immediately younger group (75- to 84-year olds).

We included patients who received at least one cycle of treatment. As a result, we missed a small number of patients who were treated palliatively because of poor performance status, frailty/comorbidities, patients' preference, and logistic issues.

As in previous studies, we observed a high early mortality rate in this elderly cohort. Overall survival from the start of first-line treatment was significantly shorter in the very elderly than in the younger age groups. However, the relative survival rate was preserved in the very elderly after an initial drop, in contrast to the pattern in younger age groups. The relative survival rate allows an estimation of the additional impact of cancer on survival and is useful, especially in groups with reduced population life expectancy and in retrospective studies in which it is often impossible to ascertain specific causes of death or to separate the effect of disease from overall decline and comorbidities.

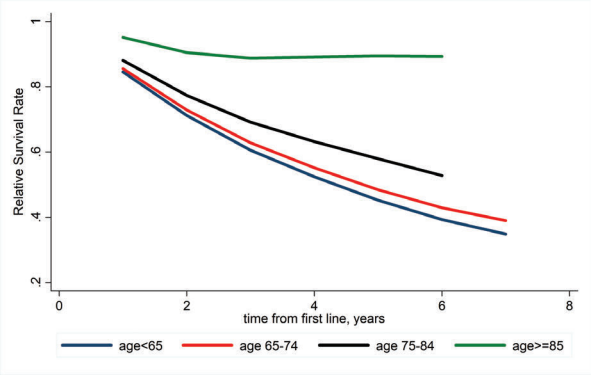

Figure 2. Relative survival rates according to age group (lowess curves).

Physicians' choice of treatment may reflect frailty, performance status, and comorbidities at presentation and this may have contributed to the poorer outcomes of patients who received alkylator-only regimens for first-line treatment. However, choice of treatment also reflects physicians' perceptions and logistic issues in delivering treatment to the very elderly. This is supported by our observation that often patients who had melphalan-prednisolone or cyclophosphamide-prednisone as first-line therapy received bortezomib or lenalidomide as second-line treatment.

Only a third of the very elderly patients received second-line treatment and a small percentage had three or more lines. This reflects reduced population life expectancy at such advanced age, patients choosing palliation and increased early mortality.

Despite the limitations of our study, our results argue in favor of actively treating very elderly myeloma patients, supported by this group's high relative survival rates. All patients included in the analysis had indications for anti-myeloma therapy reviewed at the regional multidisciplinary meetings and we assume that their outcome would have been worse had they not been actively treated. The choice of upfront therapy is crucial to improve outcomes in very elderly patients with myeloma. Adapted dosing schemes and monitoring for treatment toxicity are warranted to achieve an optimal efficacy-safety balance.

Reducing early mortality remains a challenge and more effective and less toxic regimens will further improve clinical outcomes. Myeloma treatment prevents and reverses disease-related organ damage thereby improving quality of life. The higher relative survival rate in very elderly myeloma patients compared to younger cohorts suggests that myeloma is often not a life-limiting factor for the former and frailty-adapted treatment should be routinely offered to these patients.

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