Recent major improvement in long-term survival
of younger patients with multiple myeloma

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Abbreviations: MM, multiple myeloma
SCT, stem cell transplant
Abstract

In the past, most patients with multiple myeloma (MM) died within 5-10 years following diagnosis. Within the past decade, several new therapeutic interventions have been introduced, including autologous stem cell transplant, thalidomide, lenalidomide, and bortezomib. We estimated trends in age specific 5- and 10-year relative survival of MM patients in the United States from 1990-1992 to 2002-2004 from the 1973-2004 database of the Surveillance, Epidemiology, and End Results (SEER) Program. Techniques of period analysis were employed to disclose most recent developments. Overall, 5-year relative survival increased from 28.8% to 34.7% (p<0.0001), and 10-year relative survival increased from 11.1% to 17.4% (p<0.0001) between 1990-92 and 2002-04. Much stronger increases were seen in age group <50, leading to 5- and 10-year relative survival of 56.7% and 41.3% in 2002-04, and in age group 50-59, leading to 5- and 10-year relative survival of 48.2% and 28.6% in 2002-2004. By contrast, only moderate improvement was seen in age group 60-69, and essentially no improvement was achieved among older patients. Our period analysis discloses a major increase in long-term survival of younger patients with MM in recent years which most likely reflects the impact of recent advances in therapy and their dissemination in clinical practice.
Introduction

In the past, most patients with multiple myeloma (MM) died within 5-10 years following diagnosis. Several new therapeutic interventions have been introduced for MM over the past decade. These include autologous stem cell transplant (SCT) and novel agents including thalidomide, an anti-angiogenic and immunomodulatory small molecule, lenalidomide, a derivative of thalidomide, and bortezomib, a proteosome inhibitor. All three novel agents have been shown to be active in MM, and regimens containing one of these compounds are gradually replacing chemotherapy-only regimens as standard of care in MM for patients who are not candidates for SCT\textsuperscript{1,2}. The impact of such therapeutic innovation and its dissemination on long-term prognosis should be monitored in an as timely as possible manner, but is only disclosed with substantial delay by conventional methods of survival analysis. We aimed to disclose trends from 1990-92 to 2002-04 and to derive up-to-date estimates of long-term survival of patients with MM by novel techniques of period survival analysis\textsuperscript{3,4}. Due to the differential application, efficacy and tolerance of novel therapies according to age, we were specifically interested in age specific trends of prognosis.

Methods

All data presented in this paper are derived from the 1973-2004 limited-use database of the Surveillance, Epidemiology, and End Results (SEER) Program of the United States National Cancer Institute issued in April 2007\textsuperscript{5}. Data included in the 1973-2004 SEER database are from population based cancer registries in Connecticut, New Mexico, Utah, Iowa, Hawaii, Atlanta, Detroit, Seattle-Puget Sound and San Francisco-Oakland which together cover a population of about 30 million people. Geographic areas were selected for inclusion in the SEER Program based on their ability to operate and maintain a high-quality population-based
cancer reporting system and for their epidemiologically significant population subgroups. The SEER population is comparable to the general United States population with regard to measures of poverty and education, though it tends to be more urban and has a higher proportion of foreign-born persons than the latter.

For this analysis, we selected 27,038 patients aged 15 years or older with a first diagnosis of MM (and no previous cancer diagnosis) between 1980 and 2004, who have been followed for vital status until the end of 2004. After exclusion of 58 patients (0.21%) who were reported by autopsy only and 457 patients (1.69%) who were reported by death certificate only, there remained 26,523 patients (98.10%) for the survival analysis.

Five- and 10-year survival was calculated for the calendar periods 1990-1992, 1993-1995, 1996-1998, 1999-2001 and 2002-2004 using the period analysis methodology\(^3\). Furthermore, we tested for statistical significance of trends in 5- and 10-year year survival between 1990-1992 and 2002-2004 by a recently described modelling approach\(^4\). All analyses were carried out separately for the following 5 major age groups: <50, 50-59, 60-69, 70-79, and 80+.

With period analysis, first proposed by Brenner and Gefeller in 1996\(^6\), only survival experience during the period of interest is included in the analysis. This is achieved by left truncation of observations at the beginning of the period in addition to right censoring at its end. A graphical illustration of the data included to estimate 10-year relative survival for the 2002-04 period compared to the data used to derive the most up-to-date estimate of 10-year survival from the same database using traditional “cohort analysis” is shown in figure 1. The latter would pertain to patients diagnosed in 1992-94 only and would thus not capture recent progress in therapy. It has been shown by extensive empirical evaluation that period analysis provides more up-to-date long term survival estimates than traditional “cohort-based” survival
analysis, and quite closely predicts long-term survival expectations of cancer patients diagnosed within the period of interest\textsuperscript{7,8}.

In addition to 5-year survival from diagnosis, we calculated 5-year survival in the subsequent 5 years among patients who have already survived 1, 2, 3, 4, and 5 years since diagnosis. In this way, trends and recent achievements in late survival can be analyzed specifically. They are of particular interest for MM, given the frequency of late deaths among patients with this malignancy.

According to standard practice in population-based cancer survival analysis, relative rather than absolute survival was calculated. Relative survival reflects survival of cancer patients compared to survival of the general population. It is calculated as the ratio of absolute survival of cancer patients divided by the expected survival of a group of persons of the corresponding sex, age and race in the general population\textsuperscript{9,10}. Estimates of expected survival were derived according to the so-called Ederer II method\textsuperscript{11} using US sex, age and race specific life tables\textsuperscript{12}.

All analyses were performed with the SAS software package using previously described macros for period analysis\textsuperscript{3,4}.

**Results**

Numbers of cases by age group and calendar period are shown in table 1. About half of the patients were 70 years or older, and less than 10\% were younger than 50 years at the time of diagnosis. Overall numbers of patients, as well as numbers of patients in the older age groups
were rather stable over time. However, case numbers increased by approximately half in the three youngest age groups between 1990-1992 and 2002-2004.

For all age groups combined, 5-year relative survival increased from 28.8% in 1990-1992 to 34.7% in 2002-2004, an increase of 5.9 percentage points (p-value for trend <0.0001, see table 2). More substantial increases of 11.9 and 9.4 percentage points were seen in the age groups <50 and 50-59, respectively (p=0.001 in each age group). Increases were much less pronounced in the older age groups and did not reach statistical significance. In this way the age gradient in 5-year relative survival, already visible in 1990-1992, further increased over time. In 2002-2004, 5-year relative survival ranged from 56.7% in the age group <50 to 15.2% in the age group 80+. For the two youngest age groups (<50, 50-59), the increase in 10-year relative survival from 1990-1992 to 2002-2004 was even more pronounced (+16.8 and +11.4 percent units, p<0.0001 and p=0.0001, respectively). For age groups 60-69 and 70-79 some modest increase in 10-year relative survival could still be seen, which was statistically significant for the former only. Nevertheless, 10-year relative survival remained as low as 15% and 10%, respectively, in these age groups in 2002-2004. No improvement at all could be seen for age group 80+.

A more comprehensive picture of the survival curves by age groups and their development between 1990-1992 and 2002-2004 is given in figure 2. In contrast to most other malignancies, the relative survival curves of patients with MM do not flatten out within 10 years after diagnosis, i.e., substantial excess mortality compared to the general population of the same age persists in the long run. This pattern is seen in all age groups, and it persists in all age groups even in 2002-2004, despite the major improvement in survival in the younger age groups between 1990-1992 and 2002-2004. Nevertheless, median relative survival increased from little more than 4 years in age group <50 in 1990-1992 to almost 7 years in
2002-2004. For age group 50-59, the increase in survival from 1990-1992 to 2002-2004 was mainly seen in years 5 to 10 after diagnosis.

Despite the high proportion of late deaths, conditional relative survival in subsequent five years increased gradually in all age groups with increasing time since diagnosis in 2002-2004 (see figure 3). For example, for patients who survived one year after diagnosis, the probability of surviving another 5 years was about 40% in 2002-04, compared to just over 30% in 1990-92. Patients who survived 5 years after diagnosis had a 5-year relative survival of 50% in 2002-04, compared with just under 40% in 1990-92. Thus, overall, the probability of long term survival increased in 2002-04 compared with 1990-92. In age groups <50 and 50-59, not only the overall level of conditional survival in subsequent 5 years, but also their increase with time from diagnosis was substantially higher in 2002-2004 than in 1990-1992, which indicates that reduction of excess mortality was particularly pronounced among patients who survived the first years after diagnosis.

To address the question of the timing of onset in survival improvement among the various age groups, 10-year relative survival is shown for each of the five calendar periods under investigation in figure 4. Results for the preceding time periods 1984-1986 and 1987-1989 are given for comparison. Between 1984-1986 and 1993-1995, no major improvement was seen in any of the age groups. The strong increase in 10-year relative survival in age group <50 was first seen between 1993-95 and 1996-1998 and steadily continued thereafter. The major increase in 10-year relative survival in age group 50-59 was first seen between 1996-1998 and 1999-2001 only.
Discussion

This application of period analysis to age specific long-term survival of patients with MM discloses recent major improvements in younger age groups (below age 60) which were starting in the middle and late 1990s and are ongoing since then. Not only early deaths, but especially late deaths years after initial treatment are reduced in these age groups. This way, 10-year relative survival of approximately 40% and 30% was achieved in age groups <50 and 50-59 in 2002-2004. Improvements remained much more modest and mostly non-significant in older age groups, and no improvement at all was seen in patients above 80 years of age.

To the best of our knowledge, this is the first in-depth population-based analysis of long-term survival of MM patients by age using the period analysis methodology. The relative survival figures for the 2002-04 period disclosed by this approach are higher than previously available figures\textsuperscript{13,14} and this encouraging development should be disclosed to patients, clinicians, and researchers in an as timely as possible manner. Although the period estimates of long-term survival are more up-to-date than estimates obtained by traditional cohort analysis, even the period estimates may still be somewhat too pessimistic as they still partly reflect the survival experience of patients first diagnosed and treated in earlier years. Therefore, survival expectations of patients diagnosed in 2002-04 may even be somewhat higher. This may be particularly true for older patients who may benefit from treatment with novel agents, the earliest of which were introduced in the late 1990s, more than from SCT.

Prior to the late 1990s, treatment for MM consisted of chemotherapy with or without autologous SCT rescue. Patients not eligible for SCT were classically treated with vincristine, adriamycin, and dexamethasone (VAD) or melphalan and prednisone (MP) chemotherapy\textsuperscript{1,15}. 
Although chemotherapy with these drugs can produce responses in MM, cures are essentially unheard of and 5-year survival using chemotherapy alone is very poor.

High dose melphalan with or without total body irradiation followed by autologous SCT improves survival in patients with MM\textsuperscript{16}. Prior to the early 1990s, SCT was limited to patients under 40 years of age. As improvements in SCT protocols decreased the risk of SCT, its use was expanded to more patients, with some patients as old as 75 being eligible under some current protocols\textsuperscript{17}. The combination of improvements in SCT protocols and better supportive care leading to lower treatment related mortality may account for much of the improvement in survival seen starting in the mid-1990s for patients aged <50 and in the mid- to late-1990s for patients aged 50-59 and aged 60-69. However, even with the expansion of SCT to older and less robust patients, not all patients are eligible for SCT and patients who have relapsed after SCT have few further treatment options if they are ineligible for further SCT. Additionally, SCT is rarely curative in MM, so that even patients who achieve remission with SCT may expect to need further treatment in the future. Therefore, further advances in therapy are highly desirable.

The development of novel agents for the treatment of MM in the late 1990s opened new possibilities for the treatment of patients not eligible for SCT or who had relapsed after SCT and, later, for more effective conditioning regimens for SCT. The first of these agents to undergo clinical trials was thalidomide, an anti-angiogenic and immunomodulatory small molecule. Initial clinical trials conducted in 1997-98 showed thalidomide to have activity in patients with refractory or relapsed disease, with a median event free survival of three months and overall survival of greater than 12 months for patients treated with thalidomide\textsuperscript{18}. Other studies of thalidomide in relapsed and refractory melanoma showed similar results\textsuperscript{19,20}. Later studies demonstrated that the addition of thalidomide to treatment protocols, both with and
without SCT, could improve outcomes for patients with newly diagnosed MM and that the combination of thalidomide and dexamethasone may be superior to VAD chemotherapy\textsuperscript{21-23}.

Since the approval of thalidomide for the treatment of MM, two further treatment options have appeared. A thalidomide analogue known as lenalidomide, which is effective \textit{in vitro} at lower concentrations than thalidomide and is potentially less toxic, was developed. It has been demonstrated to have efficacy in the treatment of MM, including MM previously treated with thalidomide\textsuperscript{24,25}. Bortezomib, a proteosome inhibitor, was developed in the early 21\textsuperscript{st} century. It was initially investigated in a number of malignancies and has been shown to be effective in MM\textsuperscript{2,26,27}. Currently, no single therapeutic option for patients not eligible for SCT has been shown to be clearly superior to the others, although the addition of any of the novel agents to a chemotherapeutic regimen can improve outcomes and the inclusion of one of these agents in initial treatment of MM is recommended by many in the field. Further clinical trials to clarify the use of these agents as well as to determine the best use of SCT in MM may further improve survival in this disease.

Little progress was made in the treatment of MM for patients over 70, particularly for those over 80, and only marginal progress was made for patients 60-69 during the period between 1990-92 and 2002-04. This is concerning given that the average age of diagnosis of MM is around 70 years. Elderly patients are more likely to have co-morbid medical conditions that limit their treatment options and are more likely to have a poor performance status\textsuperscript{28}. Additionally, elderly patients are underrepresented in clinical trials, therefore, less is known about the natural history and response to treatment of MM in this population than in younger patients\textsuperscript{28,29}. There is some evidence that MM may be under-treated in the elderly, even after accounting for co-morbid conditions. One cohort study of patients aged 75+ showed that treatment was given to only 72\% of patients and further chemotherapy was given to only 25\%
of patients on relapse. SCT, which is still the therapy that offers patients with MM the best chance of long term survival, is offered to elderly patients only rarely. Additionally, the prothrombotic effects of thalidomide may have led clinicians to be reluctant to use it in older patients. However, recent studies of thalidomide and bortezomib in older patients suggest that they can be used safely and effectively in this population. The combination of thalidomide with MP produced 3-year survival rates of 80% in patients aged 60-85 in one study. Notably, cardiac disease, respiratory disease, and abnormal liver or kidney function were not exclusion criteria in this study, suggesting that the results may be applicable to a broad range of older adults with MM. Therefore, progress in the treatment of older patients with MM may be seen in the next few years, as treatment with newer agents plus chemotherapy becomes more common and clinicians become more comfortable using them in older patients. Further trials which include older patients with MM are still needed to delineate the best use of SCT, chemotherapy, and novel agents in this population.

In the interpretation of our results, a number of limitations requires careful consideration. Because the SEER database does not contain information on chemotherapeutic or other medical treatment, nor on the location of treatment, the role of these factors cannot be assessed directly. Likewise, the SEER database does not contain stage information for myeloma which precludes assessment of a potential role of earlier diagnosis in improved survival. A major impact of earlier diagnosis seems unlikely though, given that no routine screening tests for MM have been introduced between the 1980s and the early 21st century.

In summary, our population-based period analysis discloses significant, major progress in the survival of MM patients since the early 1990s. Most likely, improvements in SCT and consequent extension of its use to older and less healthy patients account for the substantially improved survival in patients under 60 years of age during the 1990s and early 21st century.
The introduction of new agents in the treatment of MM provide new treatment options both for patients who can not receive SCT or have relapsed after transplant and for improved transplant protocols. With the exception of thalidomide, the newer agents were developed and approved for use in the early 2000s. Therefore, the effects novel agents may have on 5- and 10-year survival in MM is not yet maximized and further improvements in survival rates may well be seen over the next several years, particularly as the use of these agents spreads and their optimal role in the treatment of MM is established. Further research into the best treatment for older patients, including greater involvement of older patients in clinical trials, improved tolerability of SCT and increased understanding of how best to use the newer agents in older patients is needed.

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**Authors’ Contributions**

H. Brenner designed and carried out the analysis. H. Brenner and D. Pulte wrote the paper. A. Gondos critically reviewed and contributed to finalizing the paper.

**Conflict of Interest Disclosure**

The authors declare no competing financial interests.
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TABLE 1. Numbers of patients with MM by age group and calendar period

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TABLE 2. Five- and 10-year estimates of relative survival (PE = point estimate, SE = standard error) of patients with MM by age groups and calendar period

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¹ increase from 1990-1992 to 2002-2004 in percentage points
² p-value for trend from 1990-1992 to 2002-2004
FIGURE LEGENDS

FIGURE 1. Data used for estimating 10-year survival for the 2002-04 period by period analysis (closed frame). For comparison, data used to derive the most up-to-date estimates of 10-year survival from the same database using traditional “cohort analysis” is shown (dashed frame).

FIGURE 2. Ten-year relative survival curves of patients with MM by major age groups. Period estimates for 1990-1992 (solid curves) and 2002-2004 (short-dashed curves).

FIGURE 3. Conditional relative survival of patients with MM, all ages and age group <50, within subsequent years following diagnosis. Period estimates for 1990-1992 (solid lines) and 2002-2004 (short-dashed lines).

### Figure 1

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Figure 2
Figure 3
Figure 4

![Graph showing 10-year relative survival (%) by calendar period and age group (1984-1986 to 2002-2004). The graph includes lines for different age groups: <50, 50-59, 60-69, 70-79, and 80+.](image-url)
Recent major improvement in long-term survival of younger patients with multiple myeloma

Hermann Brenner, Adam Gondos and Dianne Pulte