Survival improvements in Multiple Myeloma Patients in Switzerland

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Introduction

Although a rare disease, multiple myeloma is one of the most common haematological malignancies accounting for more than 10% of all haematological cancers [1]. In Switzerland, each year around 570 individuals are diagnosed with multiple myeloma and 440 die of the disease [2]. During the last decades treatment improvements markedly increased survival of patients with multiple myeloma [3]. Successful treatment was begun in the 1960s using a combination of melphalan and prednisone achieving a median survival of 3-4 years [4, 5]. Until the 1990s, no treatment has shown further improvements in survival rates [5]. Thereafter, a new era of myeloma treatment was initiated with the introduction of high-dose chemotherapy combined with autologous stem cell transplantation [6-9] and new drugs, including thalidomide [10-12], bortezomib [13, 14] and lenalidomide [15-17]. Compared to former standard therapy, significant survival improvements of these treatments are well documented in randomized controlled trials. In addition, bisphosphonates [18-20] have shown anti-myeloma activity and a survival benefit in myeloma patients.

Clinical trials are confined to selected patients. Therefore, their results are not readily transferable to the real-life setting. However, in recent years, several observational population-based studies have shown significant improvements in survival for multiple myeloma patients in various countries [3, 21-23]. However, regional differences in health care access, health care organization, and patient management may have a substantial impact on survival. Therefore, it is important to complement clinical trials and observational data from selected patient groups with population-based epidemiological studies from different regions and countries.

We conducted an observational population-based study using cancer registry data from Switzerland to investigate survival trends in the era of high-dose chemotherapy with autologous stem cell transplantation and the first proteasome inhibitors and immunomodulatory drugs before newer treatments antibody-therapies or second generation proteasome inhibitors became widely available.

Methods

Data sources and inclusion criteria

Incident multiple myeloma cases of the years 1991-2015 and corresponding vital status information were obtained from the National Institute for Cancer Epidemiology and Registration (NICER) database. NICER is collecting and harmonizing cantonal cancer registry (CR) data and provides a central national database of cancer registration data in Switzerland. Due to the gradual introduction of cancer registration, national population coverage for this study varied from 53.5% (1991-1995) to 79.4% (2011-2015). Cantonal death rates by age, sex and calendar year were supplied by the Swiss Federal Statistical Office (SFSO), referring to all persons with permanent residence status in Switzerland.

Analytic methods

Relative survival (RS) was estimated for consecutive 5-year periods stratified by age at time of diagnosis (<65 years, 65-74 years, 75+ years) using the Ederer II method [24]. We calculated RS up to 10-years after diagnosis using period analysis for the time period 2011-2015 and conventional cohort analysis for the prior periods [24]. Significance tests for RS were applied according to the method described by Parkin and Hakulinen [25].

Results

The demographic characteristics of observed multiple myeloma cases diagnosed in Switzerland between 1991 and 2015 are presented in **Table 1**. The median age at

diagnosis remained stable throughout the observed time period with 70 years in males and 73 years in females. At time of diagnosis, around 30% each were diagnosed below the age of 65 years and between 65-74 years. The proportion of patients aged 85 and older remained stable with around 9% across all time periods (data not shown).

Tab. 1. Patient characteristics of multiple myeloma cases reported to Swiss cancer registries, 1991-2015.

	N	%
Overall	7,583	100.0%
Sex		
Males	4,072	53.7%
Females	3,511	46.3%
Age		
<65 years	2,264	29.9%
65-74 years	2,295	30.3%
>75 years	3,024	39.9%
Time period		
1991-1995	1,074	14.2%
1996-2000	1,257	16.6%
2001-2005	1,329	17.5%
2006-2010	1,713	22.6%
2011-2015	2,210	29.1%

Population covered by cancer registration: 53.4% in 1991-1995, 57.8% in 1996-2000, 58.1% in 2001-2005, 63.5% in 2006-2010 and 79.4% in 2011-2015.

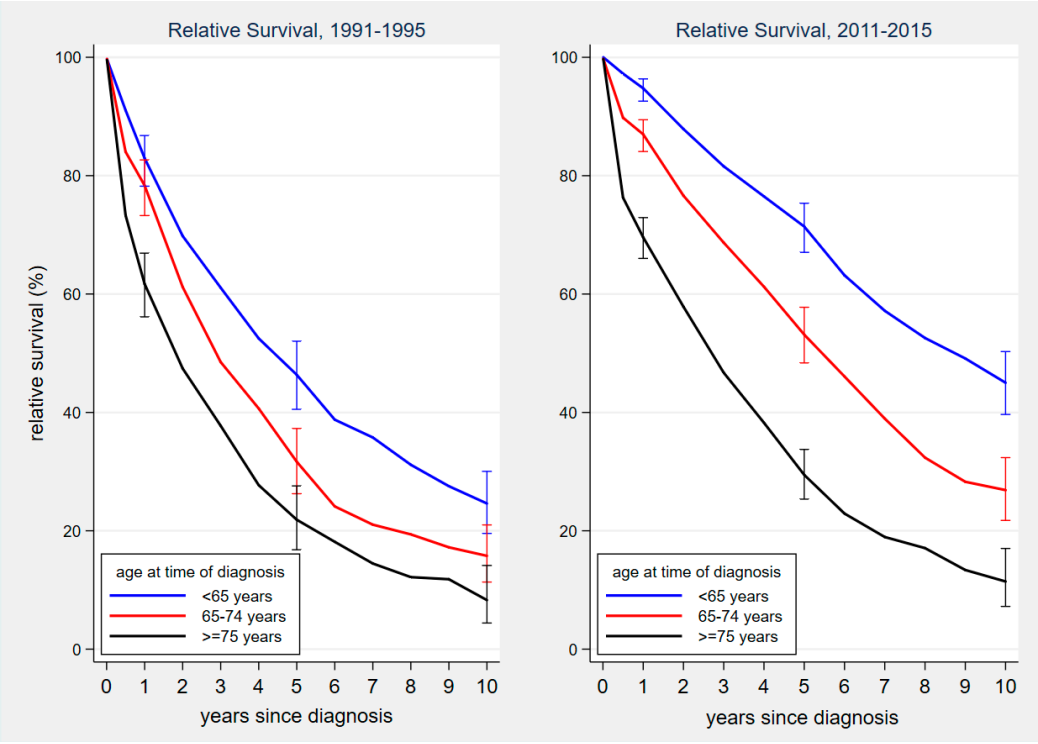
The survival curves showed an age-gradient with improved RS in younger patients (**Fig. 1**). In patients diagnosed below age 65 years, 5-year RS improved from 46.4% (95%CI 40.5-52.0) in 1991-1995 to 71.4% (95% 67.0-75.3; p<0.001) in 2011-2015 (**Fig. 1-2**). In patients diagnosed between age 65-74 years, 5-year RS increased from 31.7 (95%CI 37.3-25.7) to 53.2% (95%CI 48.4-57.8; p<0.001) and from 21.9 (95%CI 16.8-27.6) to 29.4% (95%CI 25.3-33.7; <p<0.05) in patients 75+ years old. Ten years after diagnosis, only patients diagnosed before age 65 years and patients diagnosed between age 65-74 years showed significant improvements in RS with 24.6% (95%CI 19.6-30.0) and 15.7 (95%CI 11.3-21.0) in 1991-1995 and 45.0% (95%CI 39.7-50.3; p<0.01) and 26.9 (95%CI 39.7-50.3) in 2011-2015 (p<0.05), respectively (**Fig. 1**).

Discussion

In Switzerland, relative survival of myeloma patients improved between 1991 and 2015. This improvement, however, was strongest among patients less than 65 years old, which has also been observed in previous studies [22, 23, 26].

Autologous stem cell transplantation was mainly used for patients less than 65 years of age, especially in the earlier time periods, and very rarely for patients older than

Fig. 1. Age-specific relative survival curves of multiple myeloma patients, 1991-1995 and 2011-2015.



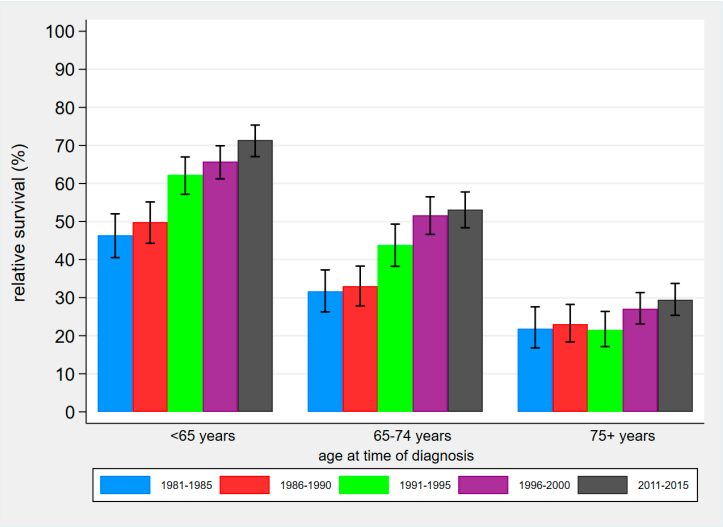


Fig. 2. Relative 5-year survival after multiple myeloma diagnosis by age-group and time period.

75 years. Hence, the steep increase in survival benefit of the younger age group might be attributed to induction treatment, high-dose chemotherapy with autologous stem cell transplantation and the new drugs, while the flatter gains observed in the older as wells as in the mid age group might be more related to the new drugs. In Switzerland, high-dose chemotherapy with autologous stem cell transplantation has increasingly been used since the 1990s for younger patients [27-34], but less frequently for patients aged 65+ years old [31, 33, 34]. The introduction of therapies over the last two decades might explain the development of survival rates over time. Zolendronic acid was approved in 2001, bortezomib for second-line treatment in 2005 and lenalidomide for second-line treatment in 2007 [35]. Thalidomide has never been approved officially, but was available through a named patient program. Notably, lenalidomide was not approved or reimbursed for first-line treatment or in combination with bortezomib nor for maintenance treatment after autologous transplantation during the whole period under observation, whereas off-label use in individual cases was possible. Newer agents were only approved in 2014 or later: pomalidomide (2014), carfilzomib (2015), panobinostat (2015), elotuzumab (2016), daratumumab (2016) and ixazomib (2017) [35]. However, early access of these drugs, especially pomalidomide and carfilzomib, within clinical trials or on individual basis in named patient programs might have been possible.

Implication on health care

Firstly, survival curves in our study did not reach a plateau, indicating the need for continuous surveillance and potentially treatment even of long-term survivors. Secondly, even among younger patients, one out of four died from myeloma within 3 years after diagnosis. Hence, despite the introduction of new drugs with remarkable results in clinical trials in the relapsed setting and an improvement of survival rates, there is still a need for improvement in first-line treatment with long-lasting deep response and excellent tolerability in the real-life setting. Thirdly, given that improvements for the middle age group and the elderly still lag behind the younger patients there is an unmet need for effective treatment strategies in these age groups.

Strengths and limitations

Our study covers a period of 25 years. Although cancer registration in Switzerland is organized on a cantonal level and not all cancer registries have covered the entire study period, a recent evaluation demonstrated high completeness across all registries and for most cancer types including multiple myeloma [36].

Conclusion

There is a trend to improved relative survival in all age groups, which is most pronounced in patients younger than 75 years. The gradient of longer relative survival from younger to older myeloma patients that has intensified over time.

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