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Impact of age, sex, ethnicity, socio-economic deprivation and novel pharmaceuticals on the overall survival of patients with multiple myeloma in New Zealand

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Summary

The impact of age, ethnicity and socio-economic deprivation in the era of novel anti-myeloma agents is unclear. Using linked national data from New Zealand, we evaluated the incidence, prevalence and overall survival (OS) of individuals who were diagnosed with myeloma between 2004 and 2016. The crude incidence rate increased from 5·42 to 8·47/100 000 and the age-standardised rate increased from 4·01 to 5·28/100 000. The estimated prevalence in December 2016 was 37·8/100 000. Median OS increased from 34·8 (95% CI 31·4, 39·3) months in 2004–2007 to 50·7 (48·5, 57·3) months in 2012–2016. Following the public funding of bortezomib in 2011, the median OS for individuals >70 years increased from 19·4 (16·3, 23·1) to 28·6 (24·5, 32·8) months. For those ≤70 years of age who did not have autologous stem cell transplantation (ASCT), median OS increased from 49·1 (37·1, 57·5) to 62·7 (51·7, 79·2) months; but for those who had ASCT, there was no difference in median OS. Socio-economic deprivation was an independent adverse prognostic factor. Māori/Pasifika and those in the most deprived quintile experienced no improvement in survival after bortezomib was funded. Our study confirms the increasing incidence and improving survival of myeloma patients, and the negative impact of Māori/Pasifika ethnicity and socio-economic deprivation on survival.

Keywords: prevalence, incidence, survival, socio-economic, multiple myeloma.

Main points

1 The age-standardised incidence rate increased between 2004 and 2016, and the incidence varied considerably by age, sex ethnic group and socioeconomic deprivation.
2 Overall survival improved following the public funding of bortezomib except for individuals who subsequently received autologous stem cell transplant and those most socio-economically deprived including Māori/Pasifika.

Multiple myeloma is a condition that predominantly affects the older population, with a median age of presentation in the 8th decade of life (Palumbo & Anderson, 2011; Jimenez-Zepeda *et al*, 2016; Blimark *et al*, 2018). As the population continues to age and patients live longer on average, both the incidence and the prevalence of multiple myeloma are expected to increase, as demonstrated in registry data from many countries (Australian Institute of Health & Welfare, 2017; Cancer Research UK, 2017; Howlader *et al*, 2018). Meanwhile, with ongoing improvement in supportive care and anti-myeloma agents, the life expectancy for these myeloma patients has also improved steadily over recent decades (Kumar *et al*, 2014). In New Zealand, the age standardised incidence rate (ASIR) has increased by approximately 30% from 1985–1989 to 2015–2016, with men having higher rates than women. Meanwhile, the median overall survival (OS) more than doubled from 1990–1994 to 2005–2009 (Sneyd *et al*, 2019).

Apart from the established disease risk factors, such as International Staging System (ISS) stage and fluorescence *in situ* hybridisation (FISH) cytogenetics, population-based studies have also found patients' characteristics, such as age, ethnicity and socio-economic status, to be independent prognostic factors (Renshaw *et al*, 2010; Costa *et al*, 2016). However, most of the data generated from these studies are based on patients treated before the widespread usage of novel

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agents or those treated in tertiary academic centres. The impact of these patient factors in the era of novel agents within a universal healthcare system is currently less well-defined.

In New Zealand, public hospital and specialist care are fully covered by the government, and all regions of the country have similar access to publicly funded anti-myeloma treatments due to the centralised funding structure. For these reasons, the treatment of multiple myeloma has been relatively homogeneous across the country, and this provides an opportunity to analyse the impact of various patient characteristics on long-term survival outcome. This purpose of this study is to evaluate trends in multiple myeloma in New Zealand, and the impact on survival with the introduction of bortezomib in a universal healthcare system at a national level.

Methods

Sources of data

Data used for this analysis were extracted initially from the New Zealand Cancer Registry (NZCR). This was established in 1948 and reporting of all new cases of malignancy became mandatory in 1994. Except when estimating prevalence, we restricted our study to cases reported after 2003 when diagnostic criteria for myeloma were unified by the International Myeloma Working Group (IMWG) (International Myeloma Working Group, 2003). All cases with a diagnostic International Classification of Diseases version 10 (ICD10) code of C90.00, C90.10, C90.01 [or ICD version 9, Australian modifications (ICD9-AM) codes 20300, 20310, 20301] diagnosed from 1 January 2004 to 31 December 2016 were included in this study and the period 2012–2016 was selected for detailed analysis. Non-residents were excluded. The definition of myeloma was revised again by the IMWG in 2014 (Rajkumar *et al*, 2014) but without changes that would have a substantial impact on our analyses. For estimating prevalence in 2016, all registrations of non-residents from January 1990 were included (see below for details).

Data collected by the NZCR include each patient's date of birth, sex, ethnicity, diagnosis, domicile code, socioeconomic status and date of death. Socio-economic deprivation was characterised by the New Zealand Deprivation Index (NZDep2013), which evaluates the socio-economic status of each domicile area based on income, home ownership, employment, qualifications, family structure, housing, access to transport, and access to communication (Atkinson *et al*, 2014). These data were categorized into socioeconomic deciles with decile 10 representing the most deprived 10% of the population and decile 1 representing the least deprived 10%. All data were anonymised centrally by encryption and approval was obtained from the New Zealand Health and Disability Ethics Committee.

The encrypted NZCR data were linked via a unique patient identifier with the following administrative databases: National Mortality Registry for cause of death; National Pharmaceutical Collection for hospital and community dispensing history; National Minimum Dataset (NMDS) for hospital admissions. First-ever hospital admissions with a principal diagnosis of myeloma in the NMDS were utilised as markers to establish the usage and date of autologous stem cell transplantation (ASCT). This marker was checked against high dosage melphalan ($\geq$140 mg/m^2; usually 200 mg/m^2) in the pharmaceutical collection, with good correspondence.

To estimate prevalence in 2016, we first counted the numbers of registrations in the period 1990 to 2016 then subtracted the number of all-cause deaths *for the same individuals* over the same time. Prior to 2000, most cases of myeloma were reported by ICD9-AM codes 20300, 20301, 20310 corresponding to ICD10-AM C90000, C9001, C9010. From 2000 onwards, some were reported with both ICD9 and ICD10 codes. Non-residents were excluded. Individuals who were not reported deceased at the last date when mortality data were available (15 February 2017) were presumed alive.

Overall survival (OS) was defined as the length of time from the date of registration to death from any underlying cause and myeloma-specific survival (MSS) was obtained by censoring deaths from other underlying causes.

Statistical analysis

The incidence of multiple myeloma was presented as a crude (unadjusted) rate, calculated by dividing the number of reported cases in the period by the population derived from the population census in 2001, 2006 and 2013 using linear interpolation between census dates and extrapolation from 2013 to 2016. The ASIR was determined using the direct method and based on the World Health Organisation (WHO) standard population (Ahmad *et al*, 2001). Confidence intervals (CIs) on incidence rates are not required because national data were used. A 2-sided *P*-value of 0·05 or less was deemed statistically significant.

Survival curves and probability of survival were analysed using the Kaplan-Meier method, and the log-rank test was used to investigate significant differences between groups. Multivariate Cox regression analysis with stepwise elimination of covariates was conducted to test the association of covariates with OS.

Results

Incidence and prevalence

Within the main study period, 1 January 2004 to 31 December 2016, a total of 3922 cases of multiple myeloma (58% male) were reported to the NZCR. The crude annual

incidence rate increased from 5·42 per 100 000 in 2004 to 8·47 per 100 000 in 2016 and the ASIR increased from 4·01 to 5·28 per 100 000 (Figure S1).

Focussing on the period 2012–2016 there were 1864 registrations (60% male) and the median age at the time of registration was 70 years (male) and 71 years (female) and lower for Māori/Pasifika than others (Table SI). The incidence rate increased steeply with age and the ASIR was 69% higher for males than females (Table I). Differences in ASIR were noted between ethnic groups, with Pasifika having the highest rate at 10·1 per 100 000 and Asians having the lowest rate at 3·5 per 100 000 (Table II). The proportions of Māori/Pasifika in the myeloma cohort were substantially higher at higher levels of socioeconomic deprivation (37% of the registrants in deciles 9/10 compared with 5% in deciles 1/2; Table SII).

We estimate that 715 women and 1059 men were living with myeloma in December 2016, a total of 1774 individuals, with prevalence rates of 45·9 and 30·0 per 100 000 population respectively (Table SIII).

Survival

Both OS and MSS improved over the 13-year period of study, with the larger increase occurring more recently. Median OS increased, from 34·8 (95% CI 31·4, 39·3) months in 2004–2007, to 50·7 (48·5, 57·3) months in 2012–2016 (Fig 1). Focussing on individuals registered with myeloma in 2012–2016, both OS and MSS were strongly age dependent (Fig 2).

In New Zealand, it is uncommon for individuals over 70 years of age to receive ASCT. Therefore, our analyses were stratified into two age groups: up to 70 years and over 70 years of age. Comparing the period 2004–2007 with 2012–2016, 5-year survival improved from 18% to 28% for the older age group, and from 54% to 62% for younger individuals (Fig 3).

Compared to other ethnic groups, median OS was inferior for Māori/Pasifika individuals ≤70 years of age but similar for those aged >70 years. Likewise, OS was inferior for high deprivation individuals (NZDep2013 deciles 9/10) aged ≤70 years but similar for those >70 years of age (Fig 4).

Table I. Age- and sex-specific mean annual incidence rates per 100 000 population for individuals registered with myeloma in 2012–2016.

Age at registration (years)	Male	Female	Total	Male/female
<50	0·81	0·54	0·68	1·52
50–59	11·95	7·00	9·40	1·71
60–69	26·72	15·87	21·17	1·68
70–79	50·59	29·82	39·68	1·70
80+	74·75	41·06	54·77	1·82
Total	9·98	6·49	8·20	1·54
ASIR	6·64	3·92	5·19	1·69

ASIR, age standardised incidence rate (Ahmad *et al*, 2001).

Survival before and after public funding of bortezomib

In May 2011, bortezomib was funded by the New Zealand government for all newly diagnosed individuals and those with relapsed disease who had never received government funded bortezomib. Lenalidomide was funded in the relapsed setting in September 2014. Median OS improved, from 38·1 months in those diagnosed in the pre-bortezomib era (January 2006 to April 2011) to 50·7 months for those diagnosed in the bortezomib era (May 2011 to December 2016) and MSS also improved (Figure S2).

The most deprived groups (deciles 9/10) had an inferior 3-year OS compared to others (0·57 vs. 0·63; $P = 0·026$) and experienced no improvement in survival following the funding of bortezomib (Figure S3), despite similar uptake of first line bortezomib (50% of patients within 14 days of registration; 95% CI 46%, 51%; $P = 0·57$) and mean cumulative dosage (65·5 mg vs. 71·4 mg; $P = 0·75$).

For those individuals ≤70 years of age who did not have ASCT, median OS increased from 49·1 months (37·1, 57·5) to 62·7 months (51·7, 79·2; $P < 0·01$); but for those who had ASCT, there was no difference in median OS [93·8 (83·0, 103·1 months; $P = 0·81$), (Fig 5)]. One factor that could contribute to these findings is that the uptake of ASCT in patients registered in 2012 to 2015 was poorer for Māori/Pasifika than European/others (30% vs. 44% at 12 months after registration; $P < 0·01$).

Multivariate analysis

In order to discern which variables contributed to survival in 2012–2016, we analysed the impact of 9 potential prognostic factors in a Cox proportional hazard model (age, sex, Māori, Pasifika, ethnicity, region, deprivation, bortezomib, ASCT) and factors that did not contribute significantly to the outcome were eliminated sequentially. Regions of New Zealand were numbered 1–4 (categorical variables) sequentially from north to south of New Zealand, with the northern cancer network region being numbered 1.

This analysis showed that age [hazard ratio (HR) 1·06, 95% CI 1·05, 1·07], socio-economic deprivation (HR 1·10, 95% CI 1·04, 1·16) and 4 regions of the country (HR 1·12, 95% CI 1·05, 1·19) were negative, and treatment with ASCT (HR 0·66, 95% CI 0·51, 0·87) or bortezomib (HR 0·74, 95% CI 0·64, 0·86) were positive, independent prognostic factors for OS. Neither sex nor ethnicity contributed independently to survival.

Discussion

As in other countries, the crude incidence of multiple myeloma in New Zealand has increased over the last 13 years (Rosenberg *et al*, 2015; Australian Institute of Health & Welfare, 2017; Cancer Research UK, 2017). This increase is partly due to ageing of the population but must also be due to

Table II. Registrations and mean annual incidence rates per 100 000 population for individuals registered with myeloma in 2012–2016 by prioritised ethnic group and sex.

	Māori	Pasifika	Asian	Eur/Other	Total
Total					
Registrations	194	111	81	1478	1864
Annual crude incidence rate	5·53	7·59	2·93	9·86	8·20
ASIR*	7·19	10·13	3·51	5·05	5·19
Male					
Registrations	104	55	46	909	1114
Annual crude incidence rate	6·06	7·61	3·41	12·32	9·98
ASIR*	8·53	10·71	4·26	6·65	6·64
Female					
Registrations	90	56	35	569	750
Annual crude incidence rate	5·02	7·58	2·47	7·48	6·49
ASIR*	6·13	9·55	2·83	3·61	3·92

Denominators: 2013 household census (New Zealand Department of Statistics)
ASIR, age standardised incidence rate (Ahmad *et al*, 2001)
*World Health Organisation standard population.

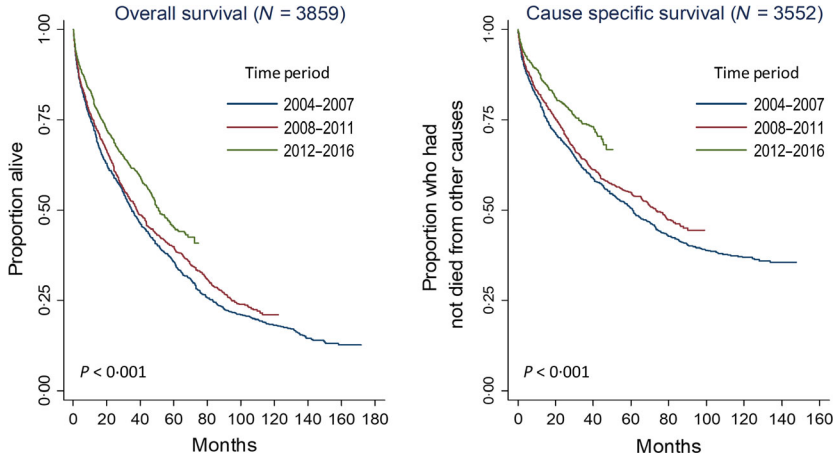

Fig 1. Overall survival and myeloma-specific survival by era in 2004–2016. [Colour figure can be viewed at wileyonlinelibrary.com]

other factors, as demonstrated by the increasing age-standardised rate. The recent update of the IMWG diagnostic criteria in 2014 (Rajkumar *et al*, 2014) would have also increased the incidence by up-diagnosing those that were previously labelled as smouldering myeloma to myeloma; however, the impact of this is likely to be small as the upward trend in incidence was already present and maintained before and after its introduction. Also, it would have no impact on OS because this was measured from registration, regardless of labelling. Amongst individuals of different ethnicity, Māori and Pasifika had a higher age-standardised incidence, were diagnosed at a younger age, and were associated with an inferior survival when compared with New Zealand Europeans and others. These findings are similar to findings published previously from New Zealand using the NZCR (Phillips & Purdie, 2007; Sneyd *et al*, 2019).

The prevalence of myeloma has not previously been reported for New Zealand. Our figure, of 1774 individuals living with myeloma in December 2016, could be an underestimate for two reasons; (i) some cases that were diagnosed prior to 1994, before reporting of cancer to the NZCR became mandatory, were not captured or were misallocated because of changes in diagnostic criteria in 2003 (International Myeloma Working Group, 2003); (ii) a small minority of younger individuals who were diagnosed with asymptomatic (smouldering) myeloma prior to 1990, or misdiagnosed, might have survived beyond 2016. A further confounder is the small proportion of individuals who could have emigrated permanently, and whose death was not recorded in the New Zealand mortality register. For example, some Pasifika individuals with terminal illness elect to return to the Pacific islands to die; although Pasifika comprise only

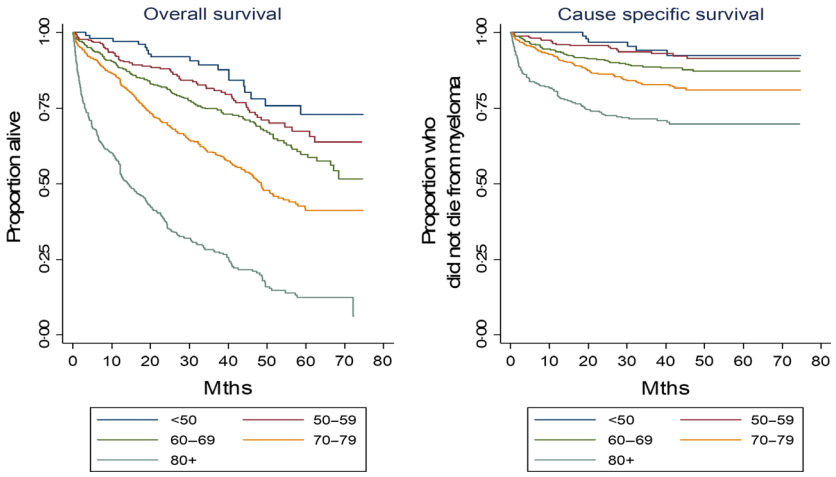

Fig 2. Overall survival and myeloma-specific survival by age group (in years) over the period 2012–2016 (N = 1864). [Colour figure can be viewed at wileyonlinelibrary.com]

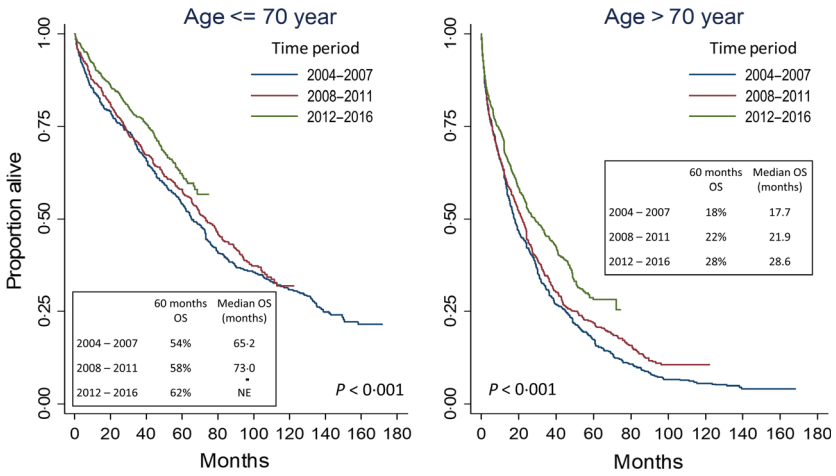

Fig 3. Overall survival (OS) by era and age group in 2004–2016 (N = 3859). [Colour figure can be viewed at wileyonlinelibrary.com]

6% of all individuals registered with myeloma, unrecorded deaths would inflate the prevalence.

OS for individuals with multiple myeloma increased over the 13-year study period, and this improvement accelerated following government funding of bortezomib in 2011. Individuals who were ineligible for transplant benefitted the most from improved access to bortezomib and this is consistent with other published real-world data (Hus *et al*, 2017; Jimenez-Zepeda *et al*, 2017; Verelst *et al*, 2018). Prior to the introduction of bortezomib, treatment options for these individuals, and those who were younger but not eligible for transplantation, would have been limited; therefore, improvement in survival seen with the introduction of bortezomib is not surprising in view of previously published prospective phase III data (Richardson *et al*, 2003; Richardson *et al*, 2005; San Miguel *et al*, 2008; Sonneveld *et al*, 2012). Other factors contributing to the improved survival could include better supportive care (Thorsteinsdottir *et al*, 2018) and funding of lenalidomide in 2014 in the relapsed setting (Dimopoulos *et al*, 2007; Dimopoulos *et al*, 2009).

Surprisingly, no improvement in survival was noted before and after bortezomib was funded amongst those who had an ASCT. This is consistent with the data published by one of the centres in New Zealand using their locally maintained database, albeit possible type II error (Hock *et al*, 2019). This may seem counter-intuitive based the published data that shows superior progression-free survival (PFS) with bortezomib induction prior to ASCT compared with conventional chemotherapy (Cavo *et al*, 2010; Rosinol *et al*, 2012; Sonneveld *et al*, 2012); however, none of these studies have demonstrated an improvement in OS, and only the updated long-term data from GIMEMA-MMY-3006, with a median

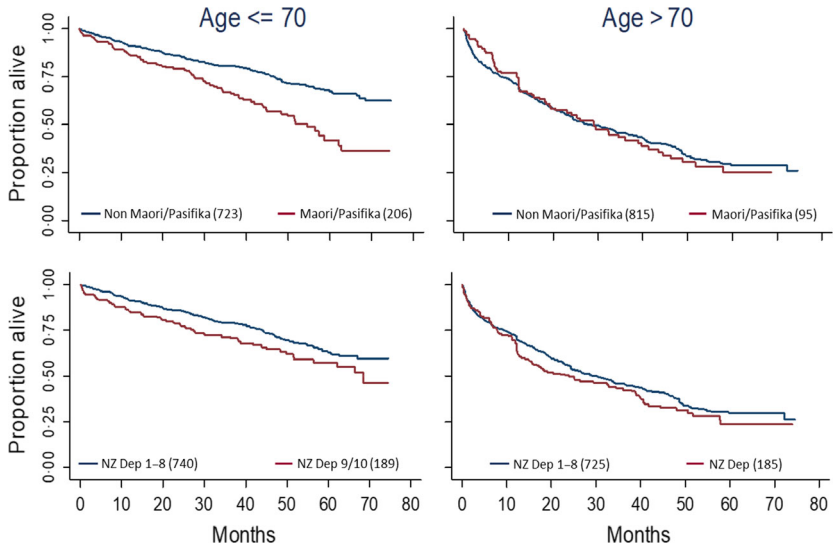

Fig 4. Overall survival for younger and older age groups stratified by ethnicity (upper graphs) and deprivation (lower graphs). Patient numbers are in parentheses. NZ Dep, New Zealand Deprivation Index. [Colour figure can be viewed at wileyonlinelibrary.com]

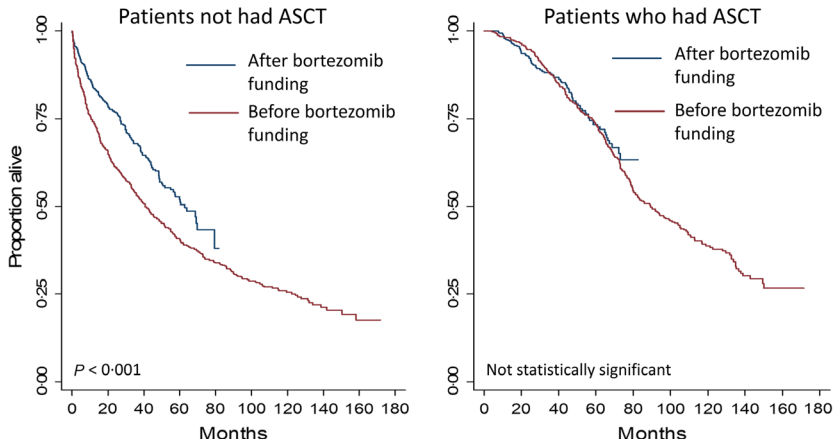

Fig 5. Overall survival before and after funding of bortezomib for individuals up to 70 years of age who did not have autologous stem cell transplantation (ASCT; N = 707 1017) and those who had ASCT (N = 709 996). [Colour figure can be viewed at wileyonlinelibrary.com]

follow-up of approximately 10 years, was able to demonstrate an improvement in OS (Tacchetti *et al*, 2018). Meta-analysis by Wang *et al* (2012) also only managed to demonstrate an improvement in PFS but not OS after evaluating the data of 1112 patients in 3 studies. These findings are in contrast to the real-world data from University Hospital Heidelberg in Germany, where novel agent induction prior to ASCT was associated with a superior OS on multivariate analysis; although data for the specific subgroup that received only bortezomib-based induction was not presented (Lehners *et al*, 2018). In addition, analysis of survival in the two periods (before and after funding of bortezomib) may be subject to selection bias due to group migration; that is, the higher response rate prior to ASCT with bortezomib-based regimen amongst the higher risk individuals would probably have led to more of these high-risk individuals to have achieved a sufficient response to proceed with ASCT than otherwise with older conventional chemotherapy. This is likely to alter the make-up of the group of individuals who received ASCT between the two time-periods and dilute the benefit seen with the introduction of bortezomib. Unfortunately, the registry does not contain the needed clinical data on individuals' cytogenetic results and stage that would allow us to explore this hypothesis further.

Our analysis suggests that the variation in survival between ethnic groups is primarily driven by differences in

socio-economic deprivation, consistent with data from the Surveillance, Epidemiology, and End Results (SEER) Program (Costa *et al*, 2016). A positive relationship between long-term survival and patient's income has been well documented in the myeloma literature (Costa *et al*, 2016; Ailawadhi *et al*, 2018), but the impact of socio-economic deprivation has been less studied. Although patient or household income is a major determining factor for socio-economic status, other aspects, such as home ownership, employment, qualifications and access to transport, are also important (Salmond *et al*, 2006). Therefore, we believe that our analysis using the New Zealand Deprivation Index provides a more comprehensive assessment of the impact of socio-economic status on the survival of individuals with myeloma than analyses of income alone. Socio-economic deprivation has often been associated with negative outcomes in individuals with malignancy, including multiple myeloma, and possible reasons include access to healthcare, delays in seeking medical attention and association with other comorbidities (Woods *et al*, 2006; Kristinsson *et al*, 2009; Fiala *et al*, 2015).

Our analysis also showed that the most socio-economically deprived individuals (NZDep2013 9/10) did not experience any improvement in survival following the funding of bortezomib, despite similar proportions of individuals being prescribed the medication compared with less deprived groups, and similar uptake and cumulative dosages. This is likely to be more complex than an issue of travel time or distance, as results from the Swedish population data also showed that the negative impact of socio-economic deprivation was independent of geographical distance from treatment centre (Kristinsson *et al*, 2009). Data from Fiala *et al* (2015) indicated that the negative impact of socio-economic status is independent of ethnicity, age, year of diagnosis, comorbidities, utilization of ASCT and insurance provider. They argue that the negative impact may be due to delays seeking medical attention, poorer tolerance and adherence to treatment, and increased treatment complications.

As this is a retrospective review of data from a centralised registry, several limitations are worth noting. First, although multivariate analysis has been performed, adjustment for confounders is likely to be incomplete. Secondly, information in the NZCR is based on data provided by the reporting pathologists without independent review to confirm the accuracy. This can potentially lead to inaccurate reporting, duplication and misallocation of cases. Previous audits comparing the data in the NZCR with a locally maintained database found that approximately 13% of the cases in the NZCR were ineligible (Stevens *et al*, 2008; Gurney *et al*, 2013). Thirdly, the registry contains limited amounts of clinical information and does not contain relevant data, such as the stage of disease and cytogenetic results. We have no information on access prior to funding, however this is likely to have been very minor because of the high cost of the drugs and because they are not covered by health insurance before they are funded.

Conclusions

Our study has one of the largest population-based cohorts of individuals with multiple myeloma treated in a universal healthcare system where the first line treatment is relatively homogeneous. OS improved over the 13-year study period, especially following the introduction of bortezomib. However, not all patient subgroups experienced the same improvement, particularly transplant eligible and/or socio-economically deprived and Māori/Pasifika, who were greatly over-represented in socioeconomic deciles 9/10. Further studies are needed to elucidate these points. Because of the possibility of confounding, these findings need independent confirmation.

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Conflict of interest

HC: Grants from Celgene, Janssen, Amgen, Roche and Beigene; Advisory board: Janssen. RM: Grant from Janssen.

Author contributions

HC drafted the manuscript. RM analysed the data. HC and RM finalised the manuscript.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Fig S1. Crude and age standardised incidence rates (ASIR) from 2004 to 2016.

Fig S2. Overall and cause-specific survival before and after bortezomib was funded on May 1, 2011.

Fig S3. Overall survival before and after funding of bortezomib, by age group.

Table SI. Age at registration in 2012–2016, by sex and ethnic group.

Table SII. Numbers and proportions of Māori/Pasifika over 30 years of age at registration with myeloma in 2012–2016, at each level of socioeconomic deprivation (NZDep2013).

Table SIII. Estimated prevalence of myeloma in December 2016 based on registrations and deaths from any cause of the same individuals in 1990–2016.

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