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The impact of recent chemotherapy innovation on the longevity of myeloma patients: US and international evidence

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ABSTRACT

The longevity of multiple myeloma patients increased sharply since the late 1990s. This increase coincided with the introduction of several important innovations in chemotherapy for myeloma. In this study, we aim to quantify the impact of recent chemotherapy innovation on the longevity of myeloma patients using both time-series US data and longitudinal data on 38 countries.

We estimate that almost two-thirds (0.99 years) of the 1997–2005 increase in the life expectancy of American myeloma patients was due to an increase in the number of chemotherapy regimens now preferred by specialists. Based on a back-of-the-envelope calculation, this means that the cost per US life-year gained from post-1997 chemotherapy innovation is unlikely to have exceeded $46,000.

We also investigate the impact of chemotherapy innovation on the myeloma mortality rate using longitudinal country-level data on 38 countries during the period 2002–2012. Countries that had larger increases in the number of chemotherapy regimens now preferred by specialists had larger subsequent declines in myeloma mortality rates, controlling for myeloma incidence. The (marginal) effect on the mortality rate of one additional preferred chemotherapy regimen is similar in other countries to its effect in the US. Non-US prices of two of the three new drugs were lower than US prices, so recent myeloma chemotherapy innovation may have been more cost-effective in other countries than it was in the US.

Recent chemotherapy innovation has had a significant positive impact on the longevity of myeloma patients in the countries in which the drugs have been available.

1. Introduction

Myeloma is a type of bone marrow cancer, where plasma cells found in the bone marrow divide uncontrollably and form tumors that can destroy bones and damage the kidneys (Harrison, 2013). The incidence varies globally from 1 per 100,000 people in China, to about 4 per 100,000 in most developed countries. Thus it is a rare disease, but it is the second most frequent malignancy of the blood in the US, where about 20,000 new cases occur every year. Median age at diagnosis is reported to lie between 61 and 70 years of age, and only 2% of patients are younger than 40 years (Cook, 2008; Raab et al., 2009). About 90% of myeloma patients have multiple myeloma (MM), which is myeloma that affects several different parts of the body.

Fig. 1 shows the age-adjusted multiple myeloma mortality rate per 100,000 inhabitants for the US population for the period 1975–2009.

After rising for about 20 years, the US MM mortality rate has fallen steadily since 1997. In this paper, we investigate the extent to which the recent decline in myeloma mortality was caused by recent innovation in chemotherapy, and whether a similar impact can also be observed in other countries.

First, we will investigate this impact using annual US time-series data during the period 1975–2009. We believe that the sharp discontinuity in the number of available chemotherapy regimens enables us to identify this impact. Second, we will investigate this impact using longitudinal country-level data on 38 countries during the period 2002–2012. In this case, identification is enabled by the fact that some chemotherapy regimens became available later in some countries than in others, or did not become available in some countries by the end of 2010.

In both approaches, the treatment variable is the (current or

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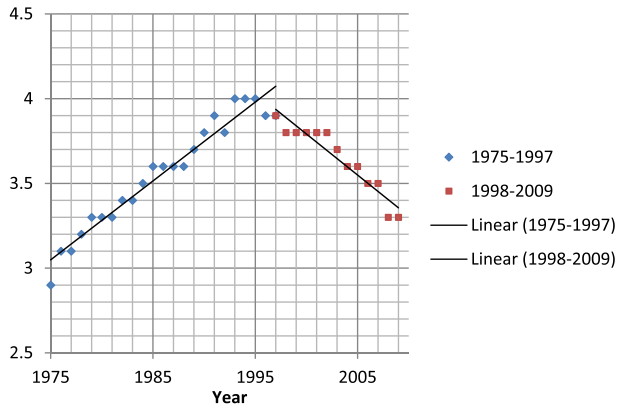

Fig. 1. US Myeloma mortality per 100,000 inhabitants based on US mortality statistics.

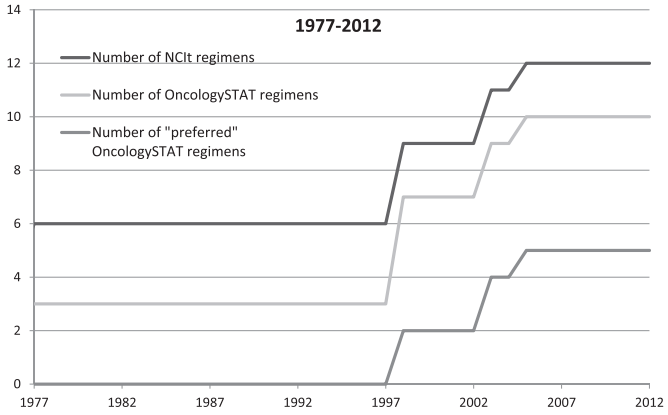

Fig. 2. Number of chemotherapy regimens that could have been used to treat American myeloma patients, 1977–2012.

lagged) *number* of chemotherapy regimens that *could* have been used to treat myeloma patients. This is not an ideal treatment measure: we would prefer to have data on the number of patients *actually treated* with each regimen. Unfortunately, data on the number of myeloma patients treated, by chemotherapy regimen and year (and country), are not available. However, there is likely to be a significant correlation between the number of available treatments and the distribution of actual treatments. If a treatment is not available, the number of patients receiving that treatment is certainly zero. Lichtenberg (2014) showed that when the number of drugs in a drug class increases, the mean vintage (FDA approval year) of drugs consumed increases.

Two reliable sources indicate that, between 1977 and 1997, there were no innovations in chemotherapy for myeloma patients and treatment options were therefore limited, but that there have been numerous innovations since 1997. The first source is the National Cancer Institute (NCI) Thesaurus database, which identifies chemotherapy regimens currently used to treat myeloma (see Appendix 1). Chemotherapy is defined as the treatment of cancer using specific chemical agents or drugs that are selectively destructive to malignant cells and tissues. The NCI Thesaurus (NCIt) also identifies the substances included in each regimen. For example, one of the regimens used to treat - myeloma is the "lenalidomide-dexamethasone regimen," which has three components: dexamethasone, bortezomib, and lenalidomide (NCIt, 2012). These three drugs were approved by the Food and Drug Administration (FDA) in 1958, 2003, and 2005, respectively (Drugs@FDA, 2012).

Therefore, 2005 is the first year in which a myeloma patient in the US could have been treated with the lenalidomide-dexamethasone regimen. Table 1 shows the regimens used to treat plasma cell myeloma, (as defined in the NCI Thesaurus and OncologySTAT) the drugs included in each regimen, the FDA approval year of those drugs, and the "regimen year": the FDA approval year of the most recently approved drug included in the regimen.

Six of the twelve regimens currently used to treat plasma cell myeloma could have been used by the year 1977. No new regimens were added during the next 20 years. Due to the approval of three new drugs (thalidomide, bortezomib, and lenalidomide), the number of available regimens doubled (from six to twelve) between 1997 and 2005 (Fig. 2). Before 1997, treatment options were quite limited, particularly for patients who relapsed. The only real treatment option available besides supportive treatments was stem cell transplantation, which was introduced in the 1980s. However, patients must be fairly young and healthy to withstand the side-effects of transplantation. Many myeloma patients therefore do not qualify for transplantation. Ramesh and Maike (2013) reports that only about 5% of myeloma patients received stem-cell transplantations in 1994. Thalidomide was the first-in-class immunomodulatory agent with an indication for multiple myeloma (MM). Thalidomide and lenalidomide target both myeloma cells and the bone marrow microenvironment (Raab et al., 2009), whereas bortezomib is a chemotherapeutic agent that induces cancer cell death by inhibiting the proteasome enzyme complex involved in cell cycle control and growth (Harrison, 2013). These agents target the immune system in such a way that patients suffer minimum damage, and normal function of the immune system remains intact (V. Kumar and Chhibber, 2011).

The second source is *The Elsevier Guide to Oncology Drugs and Regimens (2012 edition)* (also known as OncologySTAT) (Elsevier, 2012). OncologySTAT provides a comprehensive list of more than 290 commonly used single-agent and combination regimens used in the treatment of 26 cancer types. The regimens listed are those most widely used and are in accordance with guideline recommendations of the National Comprehensive Cancer Network, American Society of Clinical Oncology, and National Cancer Institute. They were selected by oncologists at major US cancer centers, including members of the OncologySTAT Advisory Board. (Appendix 2 shows OncologySTAT's website with the list of chemotherapy regimens used to treat myeloma.)

The NCIt and OncologySTAT lists of myeloma chemotherapy regimens differ in some respects. The NCIt list includes twice as many "old" (pre-1998) regimens as the OncologySTAT list: six as opposed to three. OncologySTAT also distinguishes between regimens designated by specialists as preferred for use in clinical practice and regimens that are not preferred. Preferred status may be interpreted as first-line therapies for certain groups of patients. As shown in Table 1, half of the OncologySTAT regimens are preferred regimens, and all of these are "new" (post-1997) regimens.

Although there are some discrepancies, both sources indicate that there were no innovations in chemotherapy for myeloma patients during the period 1977–1997, but that there have been numerous innovations since 1997. This is illustrated in Fig. 1, which shows annual data on the number of NCIt regimens, OncologySTAT regimens, and preferred OncologySTAT regimens that could have been used to treat myeloma patients in the US during the period 1977–2012.

In Section 2 we will review the related literature. In Section 3 we will analyze the impact of chemotherapy innovation on the longevity of myeloma patients using annual US time-series data

Table 1
National Cancer Institute Thesaurus (NCIT), Oncology STAT, and preferred Oncology STAT chemotherapy regimens.

Regimen	Drug													NCIT regimen	Oncology start regimen	Preferred oncology start regimen
	Drug year	Prednisone	Dexamethasone	Cyclo-phosphamide	Vincristine	Melphalan	Doxorubicin	Carmustine	Cisplatin	Etoposide	Thalidomide	Bortezomib	Lenalidomide			
		1955	1958	1959	1963	1964	1974	1977	1978	1983	1998	2003	2005			
	Regimen year															
MP-Myeloma	1964	X				X								Yes	Yes	No
Cyclo-phosphamide -VAD	1974		X	X	X		X							Yes	No	No
DVD	1974		X		X		X							Yes	Yes	No
VAD	1974		X		X		X							Yes	Yes	No
VBMCP	1977	X		X	X	X		X						Yes	No	No
VMCP-VBAP	1977	X		X	X	X	X	X						Yes	No	No
DT-PACE	1998		X	X			X		X	X	X			Yes	No	No
MPT	1998	X				X					X			Yes	Yes	Yes
Thalidomide - Dexamethasone	1998		X								X			Yes	Yes	No
Bortezomib - Dexamethas one	2003		X									X		Yes	No	No
MPB	2003	X				X						X		Yes	Yes	No
Lenalidomide-dexa-methasone	2005		X									X	X	Yes	Yes	Yes
DV d-T (pegylated liposomal doxorubicin, vincristine, dexamethasone, thalidomide)	1998		X		X		X				X			No	Yes	No
Thalidomide	1998										X			No	Yes	Yes
Bortezomib	2003											X		No	Yes	Yes
Bortezomib, liposomal doxorubicin	2003						X					X		No	Yes	Yes

The “drug year” is the initial year of FDA approval year of the drug.
The “regimen year” is the FDA approval year of the most recently approved drug included in the regimen.

during the period 1975–2009. In Section 4 we will analyze this impact using longitudinal country-level data on 38 countries during the period 2002–20012. Section 5 provides a summary and discussion.

2. Related literature

Numerous randomized clinical trials (RCTs) have demonstrated the efficacy of thalidomide, lenalidomide and bortezomib in the treatment of multiple myeloma. These studies provide convincing evidence of clinical efficacy for the three new agents, –showing a health benefit over a placebo or other standard of care intervention when tested in an ideal situation (Thaul, 2012). Raab et al. (2009) provide a very good overview of the clinical studies involving one or more of the advanced agents up to 2009. The evidence from these RCTs demonstrated that all three advanced agents are effective treatments for multiple myeloma (MM) in combination with standard treatment therapy or stem-cell transplantation, both in newly diagnosed patients and in relapsed and refractory MM.

In recent years clinical research has concentrated on finding the optimal substance-dose-combinations and sequencing tailored to the patient's characteristics such as age and risk factors, to avoid drug resistance (Baz et al., 2013). However, to the best of our knowledge there have not yet been any direct, head-to-head studies comparing the effectiveness of the three novel agents against each other in clinical practice (A. Kumar et al., 2011).

Partly owing to the relatively short follow-up times, only a few RCTs report outcomes in terms of overall survival (Facon et al., 2007; Hulin et al., 2007). Although not all RCTs demonstrated significant improvements in this dimension (Palumbo et al., 2006), patients receiving advanced treatment are more likely to experience at least partial response to treatment and longer time to disease progression and (adverse) event-free survival compared to standard treatment therapy (Harousseau et al., 2007). RCTs have the disadvantage that they often observe patients only while on a specific treatment and not before or after. In addition, the patient population in clinical trials is often highly selected and may not represent the patient population in clinical practice.

In contrast, the current study provides evidence on the effectiveness of three new agents as a group in real-life situations, where patients are not highly selected and represent greater regional diversity. By using a time series of aggregate cancer survival statistics and changes in the availability of advanced therapy combinations, we can include all patients, including those who switch between treatments during the observation period. In addition, since we have relatively long follow-up times (at least for US patients), we can measure outcomes in terms of overall survival and can calculate overall cost effectiveness (cost per life year gained), which is a criterion used in health technology assessments (HTA) and in many health insurance coverage decisions. The current study therefore provides evidence on the combined effectiveness of a new generation of agents comprised of two classes of medicines that affect the bone marrow environment of tumor cells through two different modes of action, rather than comparing the three agents' effectiveness against each other. Individual patient-level observational data from clinical practice may not be better suited to investigate this hypothesis, as individual data may be prone to selection bias if the patient population receiving the new chemotherapy drugs is non-random. Aggregate data are less prone to potential selection bias that could bias estimates downwards or upwards if the patients receiving the new drugs are more or less severely ill than the patient population receiving standard treatment. Compared to RCTs, our study provides real-life evidence from clinical practice.

3. Chemotherapy innovation and myeloma -longevity in the US, 1975–2009

3.1. Methods

We will analyze the impact of chemotherapy innovation on the longevity of American myeloma patients using three alternative measures of longevity and several alternative measures of chemotherapy innovation. We will do this by estimating models of the following form:

$$Y_t = \alpha + \beta\, n\_regimen_{t\text{-}s} + \gamma t + \varepsilon_t \quad (1)$$

where

Y_t = a measure of the longevity of myeloma patients in year t (t = 1975, …,2005)
$n\_regimen_{t-s}$ = a measure of the number of myeloma chemotherapy regimens that could have been used to treat myeloma patients in year t-s,
t = a time trend

The time trend (t) is included to control for the general tendency of longevity to rise throughout the sample period. Our estimation procedure will allow for first-order serial correlation of residuals.

The first measure of myeloma longevity that we will analyze is the 5-year relative survival rate (rel_surv). The second one (le) is the life expectancy of myeloma patients (mean time from date of diagnosis to date of death), and the third one is the age-adjusted myeloma mortality rate. Each of these measures has advantages and disadvantages.

Relative survival was developed to provide an objective measure of the probability of survival from cancer in the absence of other causes of death (Ederer et al., 1961). It is a measure that is not influenced by changes in mortality from other causes and, therefore, provides a useful measure for tracking survival across time. Relative survival compares the observed survival proportion of a group of cancer patients with the survival of a "similar" theoretical cancer-free group. Relative survival is formally defined as the ratio of the observed survival (all causes of death) of a cohort of cancer patients to the expected survival of a comparable set of cancer-free individuals ("SEER Cancer Statistics Review 1975–2009 (Vintage 2009 Populations): Technical Notes,")

Since rel_surv is forward-looking (rel_surv_t depends on conditional mortality rates in years t, t + 1, …, t + 4), this model implicitly incorporates a lag between the introduction of new chemotherapy regimens and conditional mortality rates (the mortality rate in year t + s, conditional on survival from diagnosis in year t until the beginning of year t + s). A lag is probably appropriate since new

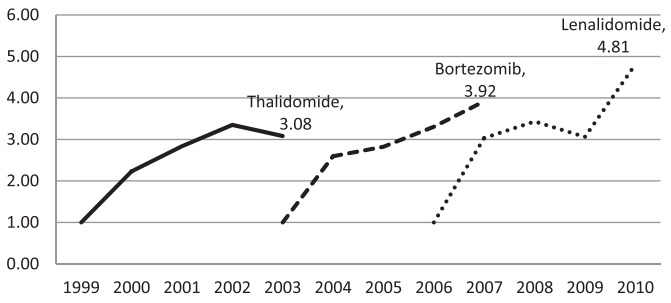

Fig. 3. Relative number of standard units sold in the US compared to 1 year after launch.
Source: Authors' calculations based on IMS Health sales data

chemotherapy regimens diffuse gradually. Fig. 3 shows the diffusion of the three new chemotherapy drugs in the US during the first five years after launch. Five years after their introduction, the drugs' sales have increased three to almost five fold compared to their sales one year after they were launched.

We will estimate eq. (1) using several alternative definitions of n_regimen: the number of NCIt regimens ($NCIt\_reg_t$), the number of OncologySTAT regimens ($OncSTAT\_reg_t$), and the number of preferred and non-preferred OncologySTAT regimens ($OncSTAT\_pref_t$ and $OncSTAT\_nonpref_t$ respectively).

The second dependent variable (longevity measure) we will analyze is life expectancy at time of myeloma diagnosis. We construct this measure using patient-level data on people diagnosed with myeloma from SEER 9 registries during the period 1973–2005. To obtain valid estimates of life expectancy (time till death) at time of diagnosis, it is necessary to account for the fact that the survival time data are right-censored (some patients were still alive on the follow-up cutoff date). We take right censoring into account by estimating parametric survival time models (using the SAS LIFEREG procedure) to obtain estimates of the mean time until death, which serves as a measure of life expectancy at time of myeloma diagnosis. Lichtenberg (2013a) used this approach to estimate the effect of pharmaceutical innovation on the longevity of elderly Americans, and Lichtenberg (2013b) used it to estimate the effect of hospital procedure innovation on the longevity of residents of Western Australia. We will assume that the number of years the patient lived after being diagnosed (or the number of years till death) follows a Weibull distribution, one of the most commonly used distributions in survival or duration time analysis. The probability density function of a Weibull random variable x is:

$$f(x;\lambda,k) = (k/\lambda)(x/\lambda)^{k-1}\exp\left(-(x/\lambda)^{k}\right) \quad x>0$$
$$= 0 \qquad\qquad\qquad\qquad\qquad\qquad x<0$$

where $k > 0$ is the *shape parameter* and $\lambda > 0$ is the *scale parameter* of the distribution, which offers a flexible way to model a wide variety of data. The mean of a Weibull random variable can be expressed as $\lambda\ \Gamma(1+(1/k))$ where $\Gamma(z)$ is the Gamma function (Kleinbaum and Mitchel, 2012):

$$\Gamma(z) = \int_0^\infty t^{z-1}e^{-t}dt$$

Estimates of the Weibull distribution parameters and related statistics, by year of myeloma diagnosis, are shown in Table 2. As expected, our Weibull distribution displays a decreasing hazard function since $k < 1$.

In addition, we will analyze the impact of chemotherapy innovation on the age-adjusted myeloma mortality rate i.e. the number of deaths whose underlying cause was myeloma per 100,000 inhabitants. (A reduction in the annual mortality rate (the probability of dying in a given year) would increase life expectancy. If the probability distribution of life expectancy (time till death) were exponential, and the rate parameter (death rate) were λ, mean time till death would be $1/\lambda$.

Unlike the previous two measures, this measure is not conditional upon a *diagnosis* of myeloma, nor does it depend on the number of people diagnosed with myeloma. Some analysts argue that not conditioning on diagnosis is desirable, since patterns of diagnosis may change over time, which could distort measures that condition on diagnosis. In particular, earlier diagnosis could introduce lead-time bias into measures like relative survival and life expectancy at time of diagnosis. McGraw-Hill Concise Dictionary of Modern Medicine (2002) defines lead –time bias "as a bias introduced into a long-term study of the efficacy of a particular therapeutic maneuver– e.g., RT or chemotherapy for malignancy – if the disease is diagnosed early–due to a newer or more sensitive diagnostic procedure or technique, the maneuver is viewed as being effective, when in fact the patient survives 'longer' because his disease was diagnosed earlier" Using data from the US and Australia, Lichtenberg (2010a) showed that, while the change in the 5-year survival rate is not a perfect measure of progress against cancer, in part because it is potentially subject to lead-time bias, it does contain useful information; especially for diseases for which development of early detection methods have been limited. According to www.cancer.org it is still difficult to diagnose MM early since symptoms often first appear when the disease reaches an advanced stage. However, if the true incidence of a disease is increasing, the age-adjusted mortality rate from the disease may rise even if there is progress in treating the disease.

Table 2
Estimates of Weibull distribution parameters and related statistics, by year of myeloma diagnosis.

Year of diagnosis	Number of patients	% of patients with right-censored survival times	Scale parameter (λ)	Shape parameter (k)	Life expectancy ($\lambda\Gamma(1+(1/K))$) in years
1975	767	1%	3.035	0.820	3.38
1976	806	0%	2.861	0.821	3.18
1977	811	0%	3.060	0.821	3.40
1978	791	1%	3.178	0.821	3.54
1979	812	0%	3.075	0.814	3.44
1980	838	0%	3.174	0.857	3.44
1981	860	1%	3.187	0.819	3.55
1982	944	1%	3.338	0.866	3.59
1983	954	1%	3.320	0.879	3.54
1984	996	1%	3.213	0.842	3.52
1985	957	1%	3.473	0.875	3.71
1986	1004	1%	3.355	0.832	3.70
1987	1136	2%	3.619	0.870	3.88
1988	1044	2%	3.505	0.895	3.70
1989	1065	2%	3.284	0.864	3.54
1990	1142	3%	3.494	0.822	3.89
1991	1235	3%	3.758	0.852	4.08
1992	1243	4%	3.433	0.838	3.77
1993	1191	5%	3.653	0.832	4.03
1994	1222	5%	3.801	0.852	4.13
1995	1251	7%	3.943	0.841	4.32
1996	1288	8%	3.848	0.798	4.37
1997	1385	8%	3.806	0.848	4.15
1998	1357	11%	4.032	0.834	4.44
1999	1321	11%	3.739	0.840	4.10
2000	1440	15%	4.090	0.843	4.47
2001	1407	18%	4.168	0.818	4.65
2002	1471	23%	4.469	0.813	5.01
2003	1472	28%	4.671	0.824	5.18
2004	1497	34%	4.841	0.793	5.52
2005	1595	40%	4.872	0.770	5.68

As noted earlier, relative survival and life expectancy at time of diagnosis are "forward looking," but the age-adjusted mortality rate is not, so we allow for a lag in the relationship between chemotherapy innovation and mortality: The appropriate lag will depend on the speed of diffusion of the new chemotherapy regimens and needs to be established empirically. For the US data, a lag of $s = 5$ years seems to fit the data best so $mort\_rate_t$ depends on $n\_regimen_{t-5}$.

All of the 1975–2009 US time-series data on myeloma that we will use to estimate eq. (1) are shown in Appendix 3.

3.2. Data

Data on rel_surv and le are based on data from the SEER 9 registries, which are located in Atlanta, Connecticut, Detroit,

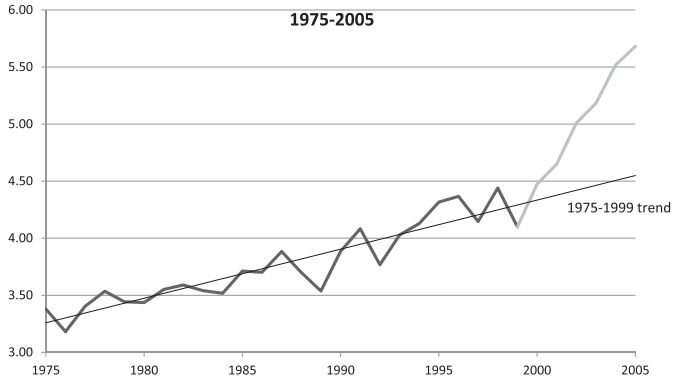

Fig. 4. Life expectancy (in years) at time of myeloma diagnosis, U.S., 1975–2005. Source: Authors's calculations based on SEER research data, 1973–2009.

Hawaii, Iowa, New Mexico, San Francisco–Oakland, Seattle-Puget Sound, and Utah. Each record in the 1973–2009 SEER research database indicates (1) the patient's date of diagnosis; (2) the Survival Time Recode, calculated using the date of diagnosis and one of the following: date of death, date last known to be alive, or follow-up cutoff date (December 31, 2009); and (3) vital status at cutoff date (1: Alive; 4: Dead). The data are publicly available for research no ethical approval was required for this study.

3.3. Results

3.3.1. Descriptive results

According to 1975–2009 data from the SEER Program, the 5-year relative survival rate in the years 1977, 1997, and 2005 were 24.7%, 32.3% and 40.9% respectively (Authors' calculations based on SEER Program 1975–2009 using SEER*Stat 8.0.1.), which means that the average annual change in the relative survival rate was almost three times as high during the period 1997–2005 as it was during 1977–1997 (Howlader et al., 2012). 2005 is the most recent year for which data on the 5-year relative survival rate were available at the time of the analysis. Estimates of life expectancy (the mean of the Weibull distribution), by year of diagnosis, are shown in Fig. 4.

Between 1975 and 1997, life expectancy increased by 0.77 years, from 3.38 to 4.15 years. Between 1997 and 2005, life expectancy increased by 1.53 years, from 4.15 to 5.68 years. The increase in life expectancy during 1997–2005 was double the increase in life expectancy during the previous 22 years; the average annual rate of increase was over five times as large during 1997–2005 as it had been during 1975–1997. Our estimates of life expectancy are broadly consistent with evidence obtained from clinical studies: "With conventional treatment, median survival is 3–4 years, which may be extended to 5–7 years or longer with advanced treatments" (Raab et al., 2009).

3.3.2. Regression results

Estimates of models of the 5-year relative survival rate, life expectancy at time of diagnosis, and the age adjusted myeloma mortality rate (eq. (1)) are presented in Table 3.

The dependent variable in models 1–3 is the 5-year relative survival rate. Model 1 includes the number of NCI Thesaurus regimens (NCIt_reg) and a time trend (Year). The NCIt_reg coefficient is positive and significant (p-value = 0.0398), indicating that the 5-year relative survival rate increased more rapidly during years when the number of NCIt regimens increased more rapidly. Between 1997 and 2005, the number of NCIt regimens increased from 6 to 12. The estimated NCIt_reg coefficient implies that this increased the relative survival rate by 4.5 percentage points (0.0075 * 6 = 0.045). This is slightly more than half of the actual 8.5 percentage point increase in the relative survival rate (from 32.3% to 40.8%).

In Model 2, we replace the number of NCIt regimens by the number of OncologySTAT regimens (OncSTAT_reg). The OncSTAT_reg coefficient is more significant (p-value = 0.0103) than the NCIt_reg coefficient and has a similar magnitude. Between 1997 and 2005, the number of OncologySTAT regimens increased from 3 to 10. The estimated OncSTAT_reg coefficient implies that this increased the survival rate by 5.0 percentage points (0.0072 * 7 = 0.050).

In Model 3, we replace the total number of OncologySTAT regimens by the number of "preferred" (by specialists) OncologySTAT regimens (OncSTAT_pref) and the number of "non-preferred" OncologySTAT regimens (OncSTAT_nonpref = OncSTAT_reg - OncSTAT_pref). The OncSTAT_pref coefficient is much larger and more significant (p-value = 0.0008) than the NCIt_reg and OncSTAT_reg coefficients. Evidently, the introduction of a preferred regimen has had a much greater impact on the relative survival rate than the introduction of a non-preferred regimen. Between 1997 and 2005, the number of preferred OncologySTAT regimens increased from 0 to 5. The estimated OncSTAT_pref coefficient implies that this increased the survival rate by 6.4 percentage points (0.0128 * 5 = 0.064). The increase in the number of preferred OncologySTAT regimens explains 75% of the 8.5 percentage point increase in the relative survival rate during 1997–2005. The coefficient on OncSTAT_nonpref is not statistically significant, indicating that the introduction of a non-preferred regimen had no impact on the survival rate.

Models 4–6 are similar to Models 1–3, but the dependent variable in Models 4–6 is life expectancy at time of diagnosis. The coefficients on NCIt_reg, OncSTAT_reg, and OncSTAT_pref are all positive and highly significant. Between 1997 and 2005, life expectancy at time of diagnosis increased by 1.53 years, from 4.15 to 5.68 years. Model 4 implies that about half (0.1245 * 6 = 0.747 years) of the increase in life expectancy was due to the increase in the number of NCIt regimens. Similarly, Model 5 implies that about half (0.1082 * 7 = 0.757 years) of the increase in life expectancy was due to the increase in the total number of OncologySTAT regimens. Model 6 includes the number of "non-preferred" OncologySTAT regimens as well as the number of "preferred" OncologySTAT regimens. The coefficient on OncSTAT_nonpref is negative and significant, suggesting that, controlling for the number of preferred regimens, an increase in the number of non-preferred regimens reduces life expectancy. (It is possible that when the number of non-preferred regimens increases and the number of preferred regimens remains constant, the probability that a patient will be treated with a non-preferred regimen increases, which could reduce survival.) However, the detrended values of OncSTAT_pref and OncSTAT_nonpref are very highly correlated (p-value < 0.0001), so distinguishing between the effects of preferred and non-preferred regimens on life expectancy is difficult. Controlling for OncSTAT_nonpref increases the coefficient on OncSTAT_pref by 61% (from 0.197 to 0.317). Model 6 implies that the net effect of increases in the number of preferred and non-preferred regimens during 1997–2005 was to increase life expectancy by 1.13 years (0.317 * 5–0.226 * 2 = 1.13).

The dependent variable in Models 7–9 is the age adjusted mortality rate, and the independent variables in models 7–9 are analogous to models 1–3 and models 4–6 respectively. (We initially controlled for the myeloma incidence rate in models 7–9, but incidence did not have a significant effect, so we report the results without incidence.) The NCIt_reg coefficient in Model 7 is

negative but insignificant (p-value = 0.1501). However, the coefficient for chemotherapy innovation using OncSTAT or OncSTAT_pref is significantly negative in Models 8 and 9, indicating that the unconditional myeloma mortality rate decreased more rapidly during years when the number of OncSTAT regimens increased more rapidly five years earlier. The estimated coefficient for OncSTAT_pref implies that the introduction of 5 new preferred OncSTAT regimens between 1997 and 2009 decreased the myeloma mortality rate by about 0.4 per 100.000 inhabitants −0.0885*5 = 0.44, which is about a 12.6% reduction in myeloma mortality given that the average myeloma mortality was about 3.5 per 100.000 inhabitants.

4. Chemotherapy innovation and myeloma mortality in 38 countries, 2002–2012

Now we will analyze the impact of chemotherapy innovation on the longevity of myeloma patients using longitudinal data on 38 countries during the period 2002–2012. The only longevity measure available for this analysis is the age-adjusted myeloma mortality rate.

4.1. Methods

We will analyze the impact of chemotherapy innovation on the age-adjusted myeloma mortality rate by estimating equations of the following form:

$$mort\_rate_{ct} = \beta\ n\_regimen_{c,t\text{-}s} + \gamma\ inc\_rate_{ct} + \alpha_c + \delta_t + \varepsilon_{ct} \quad (2)$$

where

$mort\_rate_{ct}$ = the age-adjusted myeloma mortality rate in country c in year t (t = 2002, 2012)
$n\_regimen_{c,t-s}$ = the number of chemotherapy regimens that could have been used to treat myeloma patients in country c in year t-s (s = 2, 3)
inc_rate_{ct} = the age-adjusted myeloma incidence rate in country c in year t (t = 2002, 2012)
α_c = a fixed effect for country c
δ_t = a fixed effect for year t (normalized to 0 for t = 2012)

Since it includes fixed country and year effects, eq. (2) is a difference-in-differences model. A significant negative estimate of β would indicate that countries with larger increases in the lagged number of myeloma chemotherapy regimens had larger declines (or smaller increases) in the myeloma mortality rate, conditional on the change in the myeloma incidence rate. We will allow for clustering of standard errors within countries.

4.2. Data

Data on age-adjusted myeloma mortality and incidence rates in 2002 and 2012, by country, were obtained from GLOBOCAN (http://globocan.iarc.fr/). The chemotherapy measures will be similar to the ones used in the US time-series analysis:

$OncSTAT\_reg_{ct\text{-}s}$ = the total number of OncologySTAT regimens that could have been used in country c in year t-s
$OncSTAT\_pref_{ct\text{-}s}$ = the number of "preferred" OncologySTAT regimens that could have been used in country c in year t-s
$OncSTAT\_nonpref_{ct\text{-}s}$ = the number of "nonpreferred" OncologySTAT regimens that could have been used in country c in year t-s

Construction of these variables requires information about whether each of the drugs listed in Table 1 were available in each country and year. This information was obtained from a database provided by IMS Health, which included annual data on drug sales by molecule, country, and year during the period 1999–2010. This database allowed us to determine the earliest year (starting in 1999) that each drug listed in Table 1 was sold in each country.

Appendix 4 shows the data from the Globocan database and the number of lagged chemotherapy regimens that were used for the international analyses. It includes the age standardized mortality rate per 100,000 inhabitants and the age standardized incidence rate (using the world population as reference (http://globocan.iarc.fr/Pages/glossary.aspx) and the number of lagged chemotherapy regimens available in each country in 2002 and 2012.

4.3. Results

4.3.1. Descriptive statistics

Table 4 presents summary statistics for the data used in the international analysis. On average the myeloma mortality rate declined by 0.16 while incidence increased slightly in the 38 countries included in the analysis (We included all countries for which data on myeloma mortality and incidence were available for 2002 and 2012 and for which the launch year of the three new chemotherapy drugs could be constructed from the IMS data.) Between 2002 and 2012 the average number of OncologyStat regimens increased by 3.7 and the number of preferred regimens increased by 2.6, on average.

In Fig. 5 we plot the average 2002–2012 change in mortality by the 1999–2009 increase in the number of preferred OncologyStat regimens. The chart suggests that countries that introduced more chemotherapy regimens experienced larger subsequent declines in the myeloma mortality rate.

4.3.2. Regression results

Estimates of eq. (2) are presented in Table 5. In all models, we control for changes in myeloma incidence.

In the first model (Model 10), the chemotherapy variable is the number of OncologySTAT regimens lagged by two years ($OncSTAT\_reg_{c,t-2}$). The coefficient on $OncSTAT\_reg_{c,t-2}$ is negative but insignificant; the same result is obtained when we replace the chemotherapy variable by the number of OncologySTAT regimens lagged three years (model 11). Ideally we would like to include even more lags for the chemotherapy variable, as the drugs are likely to diffuse gradually, but three years is the maximum lag possible since 1999 is the first year for which we have data on the international availability of drugs. The coefficient on inc_rate_{ct} is positive and significant in all models, indicating that the change in myeloma mortality is positively correlated with the change in (measured) incidence. In models12 and 13 we replaced the chemotherapy variable by the number of preferred OncologySTAT regimens lagged by two and three years respectively. The coefficients on $OncSTAT\_pref_{ct}$ are negative and significant in both models (p-value = 0.0463 and 0.0249) and the impact is larger after 3 years than it is after 2 years, as expected. Between 2002 and 2012, the mean value of $OncSTAT\_pref_{ct\text{-}3}$ increased by 2.6, so the estimate implies that chemotherapy innovation reduced the age adjusted mortality rate by about 0.1503 (−0.0578*2.6 = −0.1503). This means that chemotherapy decreased myeloma mortality by about 10% compared to the average level of myeloma mortality observed in 2002.

In model 14 we replaced the chemotherapy variable with the number of non-preferred chemotherapy regimens. The coefficient on $OncSTAT\_nonpref_{ct\text{-}3}$ is positive but insignificant. In model 15 we included both the number of preferred and non-preferred

Table 3
Estimates of models of the longevity of US myelon (eq (1): $Yt = a + \beta n\_regiment\text{-}s + \gamma t + \varepsilon t$.

Dependent variable	5-year relative survival rate			Life expectancy at time of diagnosis			MM Mortality rate		
Model	1	2	3	4	5	6	7	8	9
Lag (s)	0	0	0	0	0	0	5	5	5
Regressor									
Number of NCI Thesaurus regimens									
Estimate	0.00747			0.1245			−0.0281		
t Value	2.16			2.86			−1.48		
Approx Pr > |t|	0.0398			0.008			0.1501		
Number of Oncology STAT regimens									
Estimate		0.0072			0.1082			−0.0385	
t Value		2.76			3.08			−2.37	
Approx Pr > |t|		0.0103			0.0048			0.0253	
Number of "preferred" Oncology STAT regimens									
Estimate			0.0188			0.3167			−0.0885
t Value			3.9			6.16			−2.54
Approx Pr > Iti			0.0006			<0.0001			0.0176
Number of "non-preferred" Oncology STAT regimens									
Estimate			−0.0116			−0.2256			0.0486
t Value			−1.44			−2.65			0.72
Approx Pr > |t|			0.1606			0.0135			0.4755
Year									
Estimate	0.00341	0.00341	0.0035	0.0425	0.045	0.0445	0.00754	0.00883	0.0104
t Value	4.19	5.03	7.02	3.79	4.6	8.52	0.66	0.88	1.06
Approx Pr > |t|	0.0003	<0.0001	<0.0001	0.0008	<0.0001	<0.0001	0.5138	0.3467	0.2973
Intercept									
Estimate	−6.539	−6.5181	−6.647	−81.342	−85.953	−84.051	−11.416	−13.966	−17.332
t Value	−4.08	−4.86	−6.75	−3.69	−4.44	−8.16	−0.5	−0.7	−0.89
Approx Pr > |t|	0.0004	<0.0001	<0.0001	0.001	0.0001	<0.0001	0.6189	0.493	0.3825
Autoregressive parameter									
Coefficient	−0.2941	−0.3003	−0.041	−0.4319	−0.4568	−0.0036	−0.9586	−0.9509	−0.9496
t Value	−1.6	−1.64	−0.21	−2.49	−2.67	−0.02	−12.48	−11.79	−11.98
Durbin–Watson	1.8657	1.8621	1.8712	1.827	1.7833	1.9711	1.5017	1.6659	1.6468
Total R-Square	89.4%	90.0%	91.3%	92.4%	92.5%	94.1%	87.43%	88.97%	90.59%

chemotherapy regimens lagged by three years. The coefficient on $OncSTAT\_pref_{ct\text{-}3}$ is negative and significant, while the coefficient on $OncSTAT\_nonpref_{ct\text{-}3}$ is positive and significant. A possible explanation for the latter finding is that, holding constant the number of preferred regimens, an increase in the number of non-preferred regimens may increase the probability that a patient receives a non-preferred treatment. The coefficients are much larger than in the two previous models, which only included one of the chemotherapy variables. The number of preferred and non-preferred number of chemotherapy regimens are, however, highly correlated (Pearson's correlation coefficient = 0.623, $p < .0001$) so that it is difficult to disentangle their effect individually. Since the number of non-preferred regimens has on average increased by only 1.11 the combined effect of both variables ($-0.1344^{*}2.60 + 0.1954^{*}1.11 = -0.3494 + 0.2169 = 0.1325$) is comparable to the one estimated in model 13.

The estimated coefficient on $OncSTAT\_pref_{c,t\text{-}3}$ in model 13 is −0.0578 (Z = 2.24, p-value = 0.0249). When we estimate a model analogous to model 13 using U.S. time-series data, i.e. we estimate the model $mort\_rate_t = \alpha + \beta\ OncSTAT\_pref_{t\text{-}3} + \pi\ inc\_rate_{t\text{-}1} + \gamma\ t + \varepsilon_t$, we obtain a very similar estimate of β: β = −0.0503 (t = −1.90, p-value = 0.0687). (The coefficient in the US is larger and more significant when the lag is 5 years: β = −0.0701, t = −2.79, p-value = 0.0100). This implies that the (marginal) effect on the mortality rate of one additional preferred chemotherapy regimen is similar in other countries to its effect in the US.

Table 4
Summary statistics for Globocan mortality and incidence and lagged number of Oncology Stat regimens and preferred regimens.

year	N	Sample means (unweighted)			
		mort_ rate	inc_ rate	cum_ reg3	cum_ pref3
2002	38	1.50	2.14	2.74	0.16
2012	38	1.34	2.16	6.45	2.76

5. Summary and discussion

Two reliable sources indicate that there were no innovations in chemotherapy for myeloma patients during the period 1977–1997, but that there have been numerous innovations since 1997. In this paper, we investigated the impact of recent chemotherapy innovation on the longevity of myeloma patients using two different approaches. Due to data limitations, in both approaches, the treatment variable is the (current or lagged) *number* of chemotherapy regimens that *could* have been used to treat myeloma patients.

First, we investigated the impact of chemotherapy innovation using annual US time-series data during the period 1975–2009.

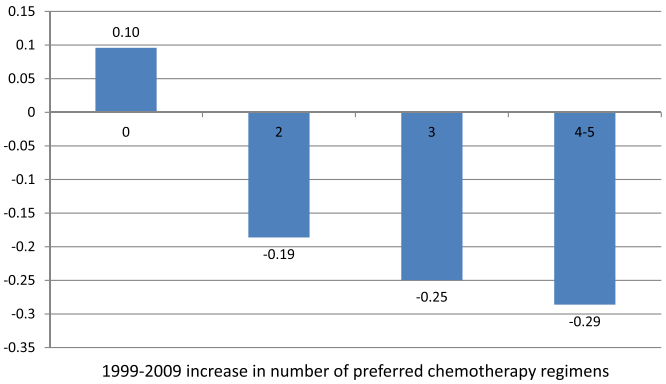

Fig. 5. Mean 2002–2012 change in mortality rate, by 1999–2009 increase in number of preferred chemotherapy regimens.

Table 5
Estimates of models of the age-adjusted myeloma mortality rate (eq. (2)) based on longitudinal country-level data, 2002–2012 All models include country and year fixed effects.

Model	10	11	12	13	14	15
Lag	2	3	2	3	3	3
Regressor						
Number of OncologySTAT regimens						
Estimate	−0.0122	−0.0127				
Z	−0.65	−0.68				
Pr > |Z|	0.5172	0.498				
Number of "preferred" OncologySTAT regimens						
Estimate			−0.05	−0.0578		−0.1344
Z			−1.99	−2.24		−3.88
Pr > |Z|			0.0463	0.0249		0.0001
Number of "non-preferred" OncologySTAT regimens						
Estimate					0.0704	0.1954
Z					1.55	2.99
Pr > |Z|					0.1202	0.0028
Incidence ASR						
Estimate	0.56	0.5515	0.1652	0.531	0.6034	0.5884
Z	3.46	3.26	3.34	3.15	4.17	4.63
Pr > |Z|	0.0005	0.0011	0.0008	0.0016	<0.0001	<0.0001
Year 2002						
Estimate	0.1273	0.1247	0.0377	0.0211	0.2506	0.0382
Z	1.57	1.58	0.57	0.33	3.08	0.57
Pr > |Z|	0.1161	0.113	0.5691	0.7386	0.0021	0.5658

The sharp discontinuity in the number of available chemotherapy regimens enables us to identify this impact. The 5-year relative survival rate increased almost three times as rapidly during the period 1997–2005 as it did during the preceding twenty years. We estimated that the increase in the number of chemotherapy regimens preferred by specialists explains 75% of the 8.5 percentage point increase in the relative survival rate of myeloma patients in the US during 1997–2005.

The average annual rate of increase in life expectancy at time of diagnosis was over five times as large during 1997–2005 as it had been during 1975–1997. In the US between 1997 and 2005, life expectancy at time of diagnosis increased by 1.53 years, from 4.15 to 5.68 years. We estimate that almost two-thirds of that increase in life expectancy was due to the increase in the number of chemotherapy regimens preferred by specialists. Chemotherapy innovation added about one-life-year per myeloma patient.

By combining the estimate of the increase in life expectancy due to chemotherapy innovation with data on myeloma incidence and drug expenditure, we can obtain a rough estimate of the incremental cost-effectiveness of (cost per life-year gained from) new myeloma treatments in the US. In 2005, the (age-adjusted) myeloma incidence rate was 6.08 cases per 100,000 population (Howlader et al., 2012). The 2005 US population was 296.4 million, so the estimated number of new myeloma cases in 2005 was 17,868 (= 6.05 * 2964.1). This estimate may be conservative: the NCI estimates that there were 21,700 new cases of multiple myeloma in the United States in 2012 (http://www.cancer.gov/cancertopics/types/myeloma). We estimate that the life expectancy of these 17,868 people was increased by almost one year, on average, by the post-1997 introduction of new chemotherapy regimens now preferred by specialists. Hence, the annual number of life-years gained from that innovation is about 17,617 (= 0.986 years/case * 17,868 cases). As shown in Table 1, all of the post-1997 chemotherapy innovations include the three new drugs: thalidomide, bortezomib, and lenalidomide. Expenditure on these three drugs probably accounts for almost the entire cost of post-1997 chemotherapy innovation to payers and patients, since other drugs included in post-1997 regimens are quite old, and they are likely to have been available in generic form and therefore inexpensive. According to IMS Health, total US expenditure on these drugs was $510 million in 2005, and $1081 million in 2010; average annual expenditure during 2005–2010 was $802 million. This implies that the cost per US life-year gained from post-1997 chemotherapy innovation was $45,551 (= $802 million/17,868 life-years gained). These figures may overstate drug expenditure because they do not account for manufacturer rebates and some of these drugs can also be used for other indications. For example, lenalidomide treats anemia caused by myelodysplastic syndrome and mantle cell lymphoma as well as multiple myeloma.

Our study includes only direct treatment costs for the new substances and no possible cost offsets of other treatment components. This may lead to overestimation of the incremental cost of treatment compared to best standard of care. Taking all treatment components into account, Goss et al. (2006) compares the cost-effectiveness of lenalidomide vs. best supportive care and finds that the incremental costs per quality-adjusted life-year (QALY) gained amount only to about 35,050 US$ in 2004, which is somewhat lower than the estimates of additional drug costs found in this study. Yet, our cost estimates are only about 15% of Aldy and Viscusi (2008) estimate ($300,000) of the average value of (willingness to pay for) a life-year in average health in the US. Unfortunately, our data do not enable us to estimate the number of QALYs per patient added by chemotherapy innovation. People with myeloma might have worse than average health. A recent cost-effectiveness study from Norway suggests that the cost per QALY is 20% higher than the cost per life-year (Moller et al., 2011). Thus, even if we adjust our estimates up accordingly (54,661 US$) our estimates indicate that the benefits of recent chemotherapy innovation exceed its costs.

In Europe and most other countries, willingness to pay for health improvements is traditionally lower than in the US. Previous studies have produced a range of estimates of the value of (or consumers' willingness to pay for) a QALY. Some of the studies were based on surveys of individuals; others relied on evidence about compensating wage differentials. The European Value of a QALY study described in Pennington et al. (2013) concluded that "a mean value ranging from $10,000 to $30,000 can be placed on one extra QALY estimated in scenarios involving certainty."

The (marginal) effect on the mortality rate of one additional preferred chemotherapy regimen is similar in other countries to its effect in the U.S. Thus, applying the average £/US$ exchange rate during the past 15 years of 0.6 £/US$ our estimates would imply that at US drug prices the average cost per QALY for new chemotherapy innovation was about 0.6 £/US$ *54,660$ = 32,800£ This is slightly above the threshold of £30.000 per QALY that the national institute for health and clinical excellence (NICE) in the UK states as the upper limit for the public reimbursement of new drugs. However, drug prices are usually much lower in Europe than in the US. Lichtenberg (2010b) estimated that, on average, UK drug prices were 64% as high as US drug prices. Data from IMS Health indicate that in 2010 non-US prices of two of the three new drugs (lenalidomide and (especially) thalidomide) were lower than US prices. Therefore, recent myeloma chemotherapy innovation may have been more cost-effective in other countries than it was in the US.

Since the survival rate and life expectancy at time of diagnosis could potentially be prone to lead-time bias, we also investigated the impact of chemotherapy innovation on the myeloma mortality rate using longitudinal data for the US and country-level data on 38 countries during the period 2002–2012. The unconditional mortality rate has the advantage that it is unaffected by potential lead-time bias that could arise if the survival of diagnosed patients only appears longer due to advances in possibilities to diagnose the disease early without extending the total lifetime of the patient.

Unfortunately information on staging of the cancer at the time of diagnosis is only available for US myeloma patients in the SEER data from 1998 to 2009. Data for the newest cohort (2009) reveal

that only 5.4% of myeloma patients are diagnosed with the disease before the cancer has metastasized to other regions of the body and treatment possibilities are still good. Since 1998, this percentage has remained rather stable, improving by less than 1% during the time when most new chemotherapy innovations reached the market. We therefore believe that it is unlikely that lead-time bias is a major issue for our analyses. In addition, our results are relatively robust across outcome measures. For the US our estimates indicate that the myeloma mortality rate per 100.000 inhabitants would have been about 12.7% higher in 2009 if the number of OncSTAT chemotherapy regimens had remained at its 1997 level.

The analysis based on international data exploits the fact that some chemotherapy regimens became available later in some countries than in others, or did not become available in some countries by the end of 2010. We found that countries that had larger increases in the number of preferred chemotherapy regimens had larger subsequent declines in myeloma mortality rates. The estimates imply that chemotherapy innovation reduced the age-adjusted mortality rate of myeloma patients by about 10% during the period 2002–2012.

Our study is relevant from a health policy perspective because our analyses of both US and international data indicate that longevity depends on access to new chemotherapy treatments. In addition, we provide evidence that there is great variation in access to new chemotherapy treatments even within industrialized countries. For example only one of the ten regimens that were available to treat multiple myeloma in Austria was available to patients in Portugal by the end of 2009. Myeloma patients in Portugal therefore can be expected to have a lower life expectancy due to poor access to new chemotherapy treatments.

In addition, the current study provides evidence on the benefits from the innovation of a class of new medicines for myeloma patients. This is interesting from a health policy perspective with regard to the speed-safety trade-off of drug safety regulation (Olson, 2008), because this class of medicines could potentially have been available to myeloma patients decades earlier. Thalidomide, the first innovation in this class of medicines, had already been marketed in Europe in the 1960s for nausea for pregnant women, but was withdrawn from the market due to severe teratogenic side effects. Decades later, scientists discovered the beneficial effect of thalidomide on the bone marrow environment of multiple myeloma (and other cancer) patients, which led to the reintroduction of the drug under strong distribution restrictions and the development of similar drugs that build on the same mechanism of action. The development and marketing of this class of drugs was impeded by an early assessment of the drug's effects and side effects for a subgroup of patients before all patient groups that could benefit from the drug had been discovered. While there have undoubtedly been welfare gains from restricting the use of thalidomide for pregnant women, our analysis indicates that the early withdrawal of that drug probably imposed welfare losses on myeloma patients.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.socscimed.2015.02.003.

References

Aldy, J.E., Viscusi, W.K., 2008. Adjusting the value of a statistical life for age and cohort effects. Rev. Econ. Stat. 90, 573–581.
Baz, R., Miladinovic, B., Patel, A., Ho, V.Q., Shain, K.H., Alsina, M., et al., 2013. Sequence of novel agents in multiple myeloma: an instrumental variable analysis. Leuk. Res. 37, 1077–1082.
http://www.cancer.gov/cancertopics/types/myeloma.
Cook, R., 2008. Economic and clinical impact of multiple myeloma to managed care. J. Manag. Care Pharm. JMCP 14, 19.
Drugs@FDA, 2012. Drugs@FDA Data Files.
Ederer, F., Axtell, L.M., Cutler, S.J., 1961. The relative survival rate: a statistical methodology. Natl. Cancer Inst. Monogr. 6, 101–121.
Elsevier, 2012. The Elsevier Guide to Oncology Drugs & Regimens: Elsevier Science Health Science.
Facon, T., Mary, J.Y., Hulin, C., Benboubker, L., Attal, M., Pegourie, B., et al., 2007. Melphalan and prednisone plus thalidomide versus melphalan and prednisone alone or reduced-intensity autologous stem cell transplantation in elderly patients with multiple myeloma (IFM 99-06): a randomised trial. Lancet 370, 1209–1218.
http://globocan.iarc.fr/.
Goss, T.F., Szende, A., Schaefer, C., Totten, P.J., Knight, R., Jadersten, M., et al., 2006. Cost effectiveness of lenalidomide in the treatment of transfusion-dependent myelodysplastic syndromes in the United States. Cancer Control 13, 17.
Harousseau, J.L., Mathiot, C., Attal, M., 2007. VELCADE/Dexamethasone (vel/D) versus VAD as induction treatment prior to autologous stem cell transplantion (ASCT) in newly diagnosed multiple myeloma (MM): updated results of the IFM 2005/01 trial. Blood (ASH Annu. Meet.) 110.
Harrison, T., 2013. Promising New Agents for Multiple Myeloma. PMLive.
Howlader, N., Noone, A., Krapcho, M., Neyman, N., Aminou, R., Waldron, W., et al., 2012. SEER Cancer statistics review, 1975-2009 (Vintage 2009 populations). In: National Cancer Institute (Ed.), Based on November 2011 SEER Data Submission, Posted to the SEER Web Site, April 2012. Bethesda, MD.
Hulin, C., F, T., Rodon, P., 2007. Melphalan-prednisonethalidomide (MP-T) demonstrates a significant survival advantage in elderly patients ≥75 years with multiple myeloma compared with melphalan-prednisone (MP) in a randomized, double-blind, placebo-controlled trial. Blood (ASH Annu. Meet.) 110.
Kleinbaum, D.G., Mitchel, K., 2012. Survival Analysis. Springer Science+Business Media, LLC.
Kumar, V., Chhibber, S., 2011. Thalidomide: an old drug with new action. J. Chemother. 23, 326–334.
Kumar, A., Hozo, I., Wheatley, K., Djulbegovic, B., 2011. Thalidomide versus bortezomib based regimens as first-line therapy for patients with multiple myeloma: a systematic review. Am. J. Hematol. 86, 18–24.
Lichtenberg, F.R., 2010a. Are increasing 5-Year survival rates evidence of Success against Cancer? a reexamination using data from the U.S. and Australia. Forum Health Econ. Policy (Health Econ.) 13.
Lichtenberg, F.R., 2010b. Pharmaceutical price discrimination and social welfare. Capit. Soc. 5.
Lichtenberg, F.R., 2013a. The effect of pharmaceutical innovation on longevity: patient level evidence from the 1996–2002 medical expenditure panel survey and linked mortality public-use files. Forum Health Econ. Policy 16, 1–33.
Lichtenberg, F.R., 2013b. The impact of therapeutic procedure innovation on hospital patient longevity: evidence from Western Australia, 2000-2007. Soc. Sci. Med. 77, 50–59.
Lichtenberg, F.R., 2014. The impact of pharmaceutical innovation on longevity and medical expenditure in France, 2000-2009. Econ. Hum. Biol. 13, 107–127.
McGraw-Hill Concise Dictionary of Modern Medicine, 2002. Lead-time Bias. The McGraw-Hill Companies, Inc.
Moller, J., Nicklasson, L., Murthy, A., 2011. Cost-effectiveness of novel relapsed-refractory multiple myeloma therapies in Norway: lenalidomide plus dexamethasone vs bortezomib. J. Med. Econ. 14, 690–697.
NCIt, 2012. NCIt's List of Substances Included in Drug Regimen Lenalidomide-dexamethasone. http://ncit.nci.nih.gov/ncitbrowser/pages/concept_details.jsf?dictionary=NCI%20Thesaurus&version=12.10e&code=C64732&type=relationship.
Olson, M.K., 2008. The risk we bear: the effects of review speed and industry user fees on new drug safety. J. Health Econ. 27, 175–200.
www.cancer.org. multiple myeloma detection.
Palumbo, A., Bringhen, S., Caravita, T., Merla, E., Capparella, V., Callea, V., et al., 2006. Oral melphalan and prednisone chemotherapy plus thalidomide compared with melphalan and prednisone alone in elderly patients with multiple myeloma: randomised controlled trial. Lancet 367, 825–831.
Pennington, M., Baker, R., Brouwer, W., Mason, H., Hansen, D.G., Robinson, A., et al., 2013. Comparing WTP values of different types of QALY gain elicited from the general public. Health Econ. 24, 280–293.
Raab, M.S., Podar, K., Breitkreutz, I., Richardson, P.G., Anderson, K.C., 2009. Multiple myeloma. Lancet 374, 324–339.
Ramesh, N., Maike, H., 2013. New Study Further Documents Trends in Stem Cell Transplantation for Multiple Myeloma. The Myeloma Beacon.
SEER Cancer Statistics Review, 1975–2009. (Vintage 2009 Populations): Technical Notes.
Thaul, S., 2012. How FDA approves drugs and regulates their safety and effectiveness. In: Congresional Research Service (Ed.).