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SPECIAL REPORT

Access to expensive cancer drugs in Dutch daily practice: Should we be concerned?

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ABSTRACT

Background: To investigate whether equal access to bortezomib has been achieved under the Dutch policy regulations that guarantee equal access to expensive inpatient drugs.

Methods: We investigated accessibility to bortezomib treatment at national and regional levels by (i) conducting interviews with stakeholders in the Dutch healthcare system to explore prescription barriers and (ii) tabulating sales data from 2004-2009 and trial participation rates.

Results: Interviews revealed awareness of the high treatment costs, although prescription barriers were not encountered. National use of bortezomib increased slowly (treating 2% of patients in 2004 to 17% in 2009), indicating a long adjustment period. Furthermore, use remains below the rate estimated by the professional association of haematologists (27%). Regional differences were found for both daily practice use (e.g. ranging from 13-27% in 2009) and clinical trial participation (e.g. ranging from 1-12% in 2006).

Conclusion: Our results were somewhat conflicting: interviews did not reveal any prescription barriers, but quantitative methods showed regional differences, signs of underutilisation, and access inequality. Investigating use and accessibility, based on data triangulation, provides valuable feedback which can enhance evidence-based decision making for both physicians and policymakers. This could improve appropriate and efficient use and ensure equal access to expensive drugs.

KEYWORDS

Cancer drugs, accessibility, regional differences, policy regulations, bortezomib, daily practice utilisation

INTRODUCTION

Increasing healthcare expenditures may result in limited and unequal access, particularly with regard to new and innovative cancer drugs with high acquisition costs. Policymakers have to make reimbursement decisions considering both rapid and equal accessibility to promising drugs as well as the scarcity of resources. Usually, guaranteeing rapid access means making decisions while available evidence on clinical- and cost-effectiveness is limited.[1] One way of dealing with the need for rapid access and limited evidence is the 'coverage with evidence development' policy; reimbursement under the condition that additional research will be conducted.[1,2]

Such policies have been implemented in several countries for surgical procedures, medical devices and pharmaceuticals.[2] Over the last decade, a coverage with evidence development policy was also initiated in the Netherlands, partly triggered by signs of underutilisation and 'zip code prescribing' of trastuzumab.[3] Early access to expensive inpatient drugs is linked with the obligation to gather data on appropriate drug use and cost-effectiveness in daily practice.[4] Drugs meeting the criteria of added therapeutic value and expected budget impact of at least 2.5 million were temporarily included in the policy of 2006-2012. Four years after inclusion, a reassessment will determine whether or not additional financing should continue to exist. At the time we conducted our study, hospitals received 80% of its acquisition costs if a drug was included.[5]

Currently more than 30, mostly cancer, drugs are included in this policy. One of these drugs is bortezomib, used for treating multiple myeloma (MM). MM is the second most common haematological cancer. The five-year prevalence in Western Europe is 31,056 while the annual age-standardised incidence rate is 3.2 per

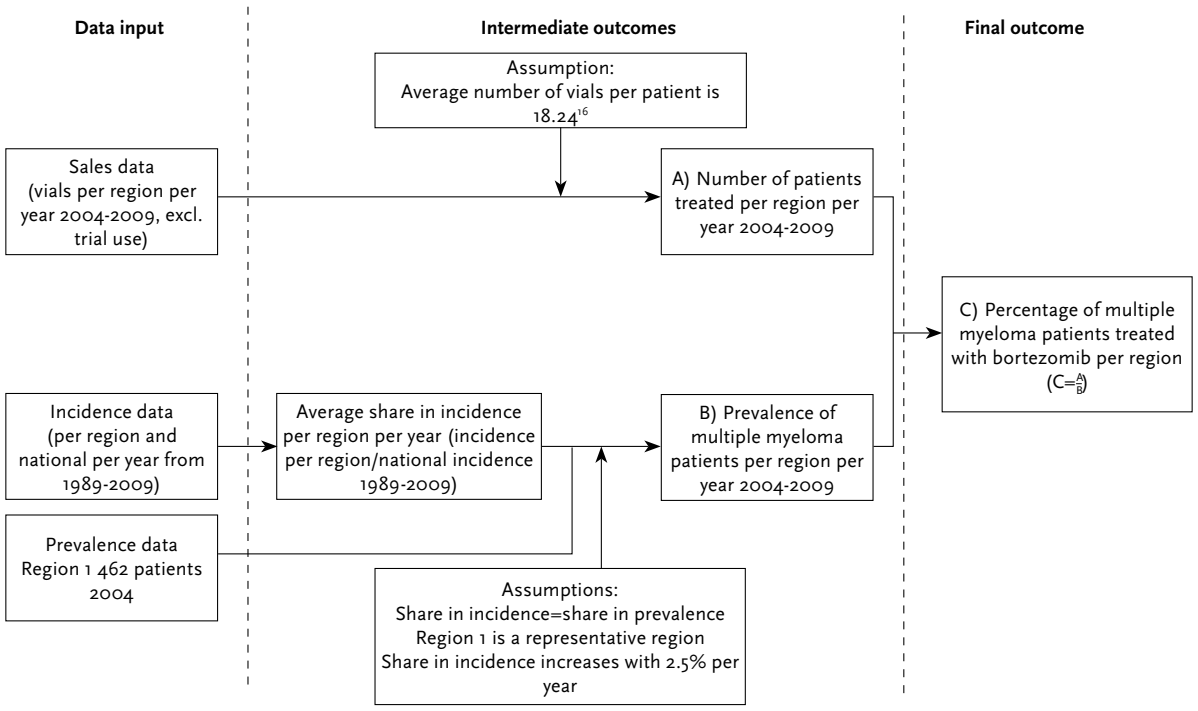
100,000 (IARC GLOBOCAN 2008). Bortezomib obtained European Medicines Agency (EMA) approval in 2004 by demonstrating superior efficacy compared with chemotherapy for the treatment of advanced MM;[6-8] it was included on the Dutch expensive drug list in 2006. Advances in MM treatment in the past decade significantly increased overall survival (44.8 vs 29.9 months[9]), which was largely due to the introduction of autologous stem cell transplantation and new therapeutic agents including thalidomide, lenalidomide, and bortezomib.[9,10] While thalidomide is relatively inexpensive, bortezomib and lenalidomide are expensive drugs. Both are incorporated in professional guidelines.[11] However, the orphan status granted to lenalidomide results in 100% reimbursement for lenalidomide compared with an 80% of reimbursement for bortezomib during our study period. Consequently, accessibility might be an issue, especially for bortezomib.
Previous research studied accessibility and use of expensive drugs in the Netherlands;[12,13] however, it remains unclear whether the Dutch policy actually guarantees equal access to expensive inpatient drugs. We investigated whether equal access to bortezomib has been achieved in the Netherlands. We analysed bortezomib use patterns by means of aggregate sales data and conducted interviews to shed light on perceived or real prescription barriers.

MATERIALS AND METHODS

We took a two-pronged approach. First, seven in-depth interviews were conducted to qualitatively investigate the existence of accessibility issues and prescription barriers. Interviewees were representatives of stakeholders in the Dutch healthcare system: (i) a representative of the Dutch Healthcare Authority (NZa), (ii) a representative of the Healthcare Inspectorate (IGZ), (iii) a hospital director of finance, (iv) four haematologists from hospitals varying in size and country location (the North-West, East, South-West, and South). Respondents were selected based on their involvement and knowledge of expensive inpatient drug regulations (NZa and IGZ) or geographical location and type of hospital (haematologists and director of finance). All semi-structured interviews were recorded and analysed according to the steps of Creswell,[14] including transcription, coding, interpretation, and description.
Second, we quantitatively investigated the use of bortezomib in daily practice. Because data on bortezomib use at the individual patient level are not available, we combined Dutch sales data (excluding use in clinical trials) from 2004-2009 from the manufacturer, Janssen Pharmaceutical Companies of Johnson & Johnson, with incidence and prevalence data from the Netherlands Cancer Registry.[15] *Figure 1* provides the flowchart of data used, intermediate and final outcomes and the underlying assumptions.

To estimate the number of treated patients ((A) in *figure 1),* the number of vials sold was divided by the average number of vials used per patient. The average number of vials per patient (18.24) was based on a Dutch observational study of 72 bortezomib patients treated in daily practice from 2004-2008.[16]
To investigate bortezomib use across regions, we used the regional division of the nationwide Netherlands Cancer Registry distinguishing eight Comprehensive Cancer Centres.[15] Since these regions differ in size, prescription rates were expressed relative to the number of patients per region. We assumed that equal accessibility to bortezomib would be achieved if the proportion of vials used per region was similar to their proportion of national incidence or prevalence. Regional shares in incidence were calculated over the years 1989-2009. For example, the share in incidence in 2009 for Comprehensive Cancer Centre Amsterdam (IKA) was 18.8%. We calculated this percentage by dividing the incidence of IKA (201) by the national incidence (1069).
Because prevalence numbers were only available for IKA (462 patients in 2004) for one year, we estimated other regional prevalence (B) from their relative shares in incidence. Hereby we assumed (i) IKA to be representative for the other regions and (ii) the share in incidence per region is equal to the share in prevalence (e.g. if IKA has 19% of the incidence it will also have 19% of the prevalence), and (iii) an annually increasing prevalence of 2.5% (average annual increase over the years 1989-2009[15]) per year because of rises in incidence.[10] Detailed additional information about incidence and prevalence estimates per year is available from the authors upon request.
To obtain a regionally comparable percentage of treated patients (C), we divided the estimated number of treated patients (A) by the estimated prevalence (B). To put regional percentages in perspective, we compared our computed use with the expected percentage of MM patients eligible for bortezomib treatment as estimated by the Dutch professional association of haematologists (the Dutch-Belgian Cooperative Trial Group for Haematology and Oncology (HOVON)). HOVON estimated that about 1600 patients would be eligible for MM treatment per year. Of these patients, one-third would not qualify for treatment with either bortezomib or lenalidomide due to age, the patient's condition or preferences. As result, 1070 patients are eligible for advanced therapy each year.[5] Since patients treated with bortezomib might also be eligible for treatment with lenalidomide and vice versa, HOVON assumed that the number of patients treated with each drug would be similar (50%). To compare the HOVON estimation with the proportion of patients treated with bortezomib per region, we divided the 535 eligible patients (i.e. 1070 divided by 2) by HOVON's estimated prevalence (i.e. 2000 patients), resulting in an estimation of 27% patients.

Figure 1. *Flowchart of data input, intermediate and final outcomes*



Furthermore, since bortezomib was a novel treatment, clinical trials were conducted during our years of investigation. Because MM patients are often included in clinical trials, relatively high or low trial participation could distort our computed daily practice use and identified regional differences. Therefore, we selected the two largest clinical studies including bortezomib during our investigated time period and studied trial participation at the regional level. Calculation methods were similar: we divided the number of patients included in trials by regional prevalence to obtain regional trial participation rates for the years 2005-2009. We then combined trial participation with regional daily practice use to compare similarities and differences across regions.

RESULTS

Interview results

Interviewees of the NZa and IGZ did not reveal any accessibility issues for expensive drugs. The IGZ representative, however, admitted that the body had no active role in investigating such issues.

Hospitals regulate financial management in various ways. As a result, it may differ per hospital who is responsible for the budget and who is making the financial decisions. According to the interviewed physicians, their financial department divided the total hospital budget by department, whereas physicians organised the division and implementation of the budget within departments. These assumptions were verified and confirmed by the hospital financial manager. Based on these results, we concluded that in the studied hospitals financial management, of both treatment decisions and organisation of care, was the physicians' responsibility.

Generally, all physicians agreed that access to bortezomib is guaranteed in the Netherlands for patients in need. The existence of strict quantitative restrictions was explicitly denied. Physicians adhered to professional guidelines as far as treatment is concerned, which were frequently mentioned as important. Consultation with colleagues and patient characteristics also seemed to be important factors in the decision (how) to treat. Apart from some variation immediately after the introduction of bortezomib, respondents believed that all eligible patients had equal access.

The Dutch policy of 2006-2012 aimed to facilitate prescription and guarantee access while maintaining incentive for efficiency. According to haematologists, the effects of this policy were two-sided. An additional budget of 80% facilitated prescription but the remaining 20%, financed from the general hospital budget, could hinder prescription. The policy was therefore perceived as ambiguous: while the government relieved the high financial burden, the remainder still had to be financed from the general hospital budget. The situation stimulated local initiatives to manage access to expensive drugs, resulting in a local expensive drug committee to judge

appropriate use and structures for consultations with more experienced physicians. Although expensive drugs were perceived as a high financial burden, according to the respondents, budget played no role in treatment choices.

Data results

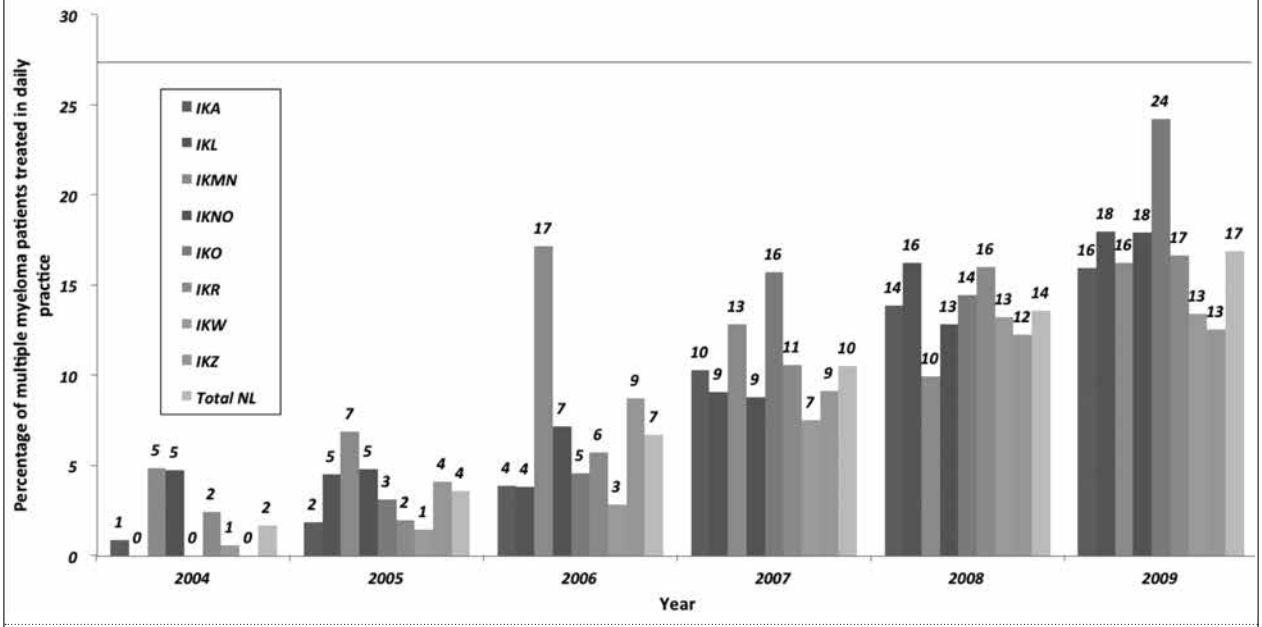
Daily practice use. *Figure 2* presents the percentage of patients treated with bortezomib from 2004-2009 irrespective of treatment line. As mentioned in the method section, HOVON estimated that 27% of MM patients are eligible for bortezomib treatment in daily practice. This is presented as a horizontal line in *figure 2*. *Figure 2* reveals relatively low use in 2004 and 2005 for all regions, which was expected since bortezomib was then an innovative treatment and not included on the expensive drug list until 2006. Three regions did not use bortezomib in 2004; all regions used it in 2005. Differences across regions exist in all years with no stable pattern; sometimes regions switched from a high prescription rank in 2005 and 2006 to a low one in 2008. In 2008, two years after inclusion on the expensive drug list, differences between the regions decreased. In 2009, Comprehensive Cancer Centre East (IKO) was the highest prescribing region and Comprehensive Cancer Centre South (IKZ) the lowest, revealing that in one region 24% of patients received bortezomib while in another only 13% received bortezomib. In all regions the prescription rate was below the 27% of eligible patients as estimated by HOVON.

Use in trials. *Figure 3* shows the participation in the HOVON 65[17] (phase I/II study) and HOVON 86[18] study (Phase III randomised controlled trial) per region in the 2005-2009 period. We observed different trial participation rates and, as *figure 3* illustrates, trial participation increased from 2005-2007, and decreased in 2008 to almost no participation in 2009. A comparison of *figures 2* and *3* reveals that the percentage of patients treated in trials is lower than daily practice use of bortezomib.
Finally, *figure 4* presents the regional percentages of treated patients aggregated over the years 2005-2009. Comprehensive Cancer Centre Netherlands Central (IKMN) had the highest daily practice use and trial participation (19% were either treated with bortezomib or included in one of the larger trials); IKZ had the lowest (10%). *Figure 4* also shows that although differences remain, the fluctuation reduced over time. In general, regions with above average daily practice use also had above average trial participation rates.

DISCUSSION

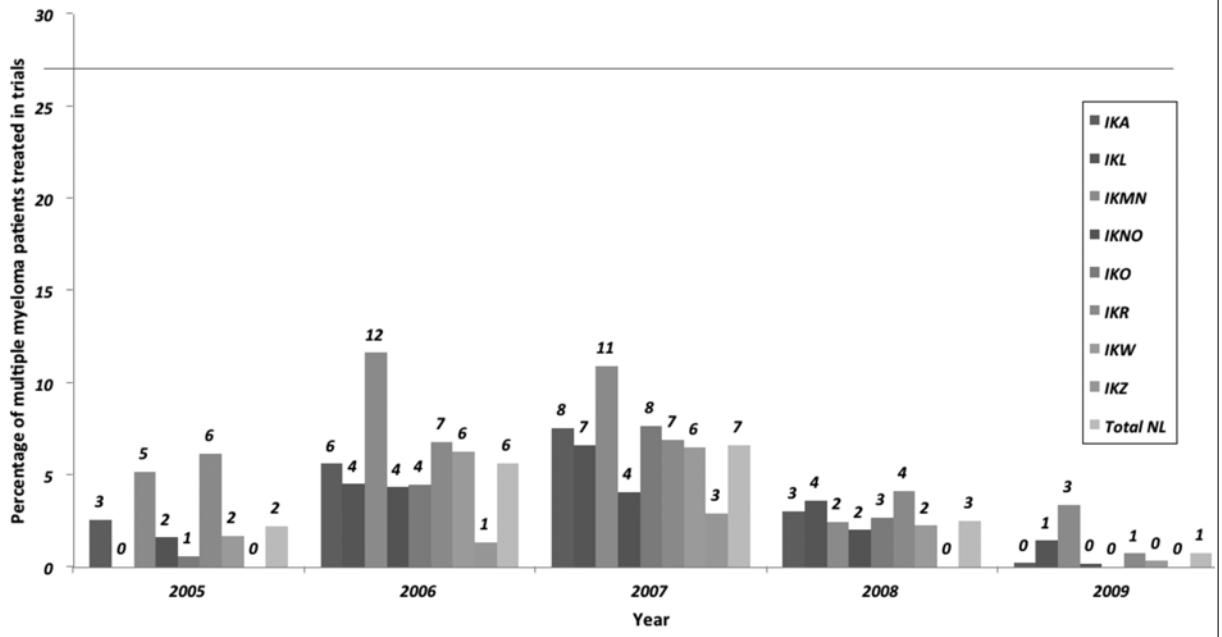
The aim of our study was to investigate whether bortezomib treatment conformed to policy regulations that were designed to guarantee equal access to expensive inpatient drugs in the Netherlands. Interviews revealed that physicians feel some financial pressure but do not

Figure 2. *Percentage of multiple myeloma patients treated in daily practice (not in a clinical trial) with bortezomib per region from 2004-2009*



IKA = Comprehensive Cancer Centre Amsterdam; IKL = Comprehensive Cancer Centre Limburg; IKMN = Comprehensive Cancer Centre Netherlands Central; IKNO = Comprehensive Cancer Centre North East; IKO = Comprehensive Cancer Centre East; IKR = Comprehensive Cancer Centre Rotterdam; IKW = Comprehensive Cancer Centre West; IKZ = Comprehensive Cancer Centre South.

Figure 3. *Percentage of multiple myeloma patients treated in clinical trials (HOVON 65 and HOVON 86) per region from 2005-2009*



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experience prescription barriers and believe that access to expensive cancer drugs is guaranteed. In addition, at that time there were no signs of accessibility issues among IGZ and NZa. Our results, however, also showed that (i) after the introduction of bortezomib, it took one to two years before the drug was prescribed regularly in all regions; (ii) the percentage of patients treated is below the expected 27% of eligible patients; and (iii) there are unexplained regional differences.

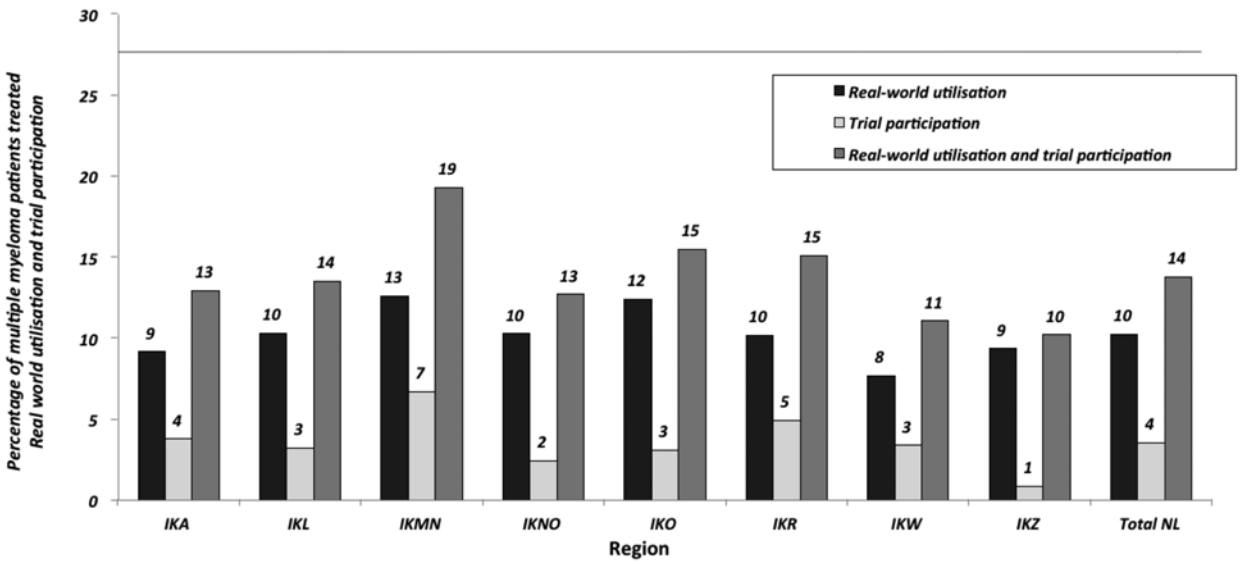
In order to investigate accessibility issues and compare regional use levels we had to make several assumptions, especially to calculate the percentage of MM patients treated with bortezomib. While the regions defined by the Dutch cancer registry vary in size, population and available hospital facilities, we expect the baseline patient characteristics to be comparable across regions. Since accurate prevalence numbers were unavailable, we assumed prevalence could be obtained from the distribution of incidence after verifying that the regional distribution of incidence was stable over a long period with a maximum deviation of only 3%. Some uncertainty surrounding total prevalence, however, remains.

Although these assumptions influence the percentage of patients treated, we believe our conclusion of low prescription rates will not be effected. Levels of use would only be closer to HOVON's expected use of 27% if the prevalence of multiple myeloma was much lower (i.e. less than 1700 patients). Considering incidence is 1100 patients per year, prevalence of less than 1700 seems highly unlikely.

Nevertheless, the share in incidence per region was remarkably stable, confirming a stable division between the regions over time. If prescription rates per region were similar, we expected the regions to be accountable for a similar share in bortezomib as their share in incidence. Therefore, regional variation was definitely established, although violations of our assumptions could enlarge or reduce the differences.

Observed regional variation, in both daily practice and trial use, indicates either differences in prescription behaviour or referral of patients to, for example, more experienced hospitals. Because we used sales data aggregated per hospital, we cannot distinguish between patients living in the region and patients referred to the region. Both causes – prescription behaviour and patient referral – limit accessibility. IKZ may have been especially sensitive to regional border crossing because it is the only region without an academic hospital. In this region, use and trial participation is low while relatively high numbers are observed in its neighbouring region (i.e. IKMN). Bortezomib administration, however, does not require specialised skills or hospital facilities, implying that expertise may have been a valid reason for referral immediately after the introduction in 2004, but should be of minor importance in subsequent years.

Figure 4. *Percentage of multiple myeloma patients treated in daily practice and clinical trials 2005-2009*



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We studied treatment patterns at an aggregated level, hence neglected other treatment options such as thalidomide and lenalidomide. Because thalidomide is relatively inexpensive in the Netherlands, accessibility should not be an issue. Lenalidomide was accepted for reimbursement at the end of 2007 in Dutch daily practice, creating a competitive alternative treatment option for the years 2008 and 2009 in our analyses. However, lenalidomide does not compensate the low levels of bortezomib prescription. In 2007, 75 patients were treated with lenalidomide and this number increased to 452 and 671 in 2008 and 2009, respectively.[5,19]

Regional differences and under-provision have been previously reported in the Netherlands. Large regional differences and under-provision of trastuzumab in the Netherlands were, according to the Dutch Breast Cancer Association,[3] mainly due to cost. After the accessibility issues of trastuzumab, the Dutch policy for expensive drugs was revised in 2006. Although bortezomib has been on the market since 2004, it was not until it was admitted to the expensive drug list in 2006 that its use in daily practice doubled compared with the previous year. The increase might indicate that the implemented policy facilitated prescription. Other developments occurred simultaneously, however, including changes in professional guidelines that recommended bortezomib in earlier treatment phases. The relatively low use in the first years might have been caused by a long adjustment period of physicians who needed to be familiarised with a new drug.[20,21] Bortezomib was, apart from the re-introduction of thalidomide, the first new innovative treatment option for multiple myeloma patients in four decades. It is important that physicians and policymakers are aware of such lags in the regular use of a new innovative and effective drug. Their implementation should receive more attention to accelerate diffusion by, for example, providing feedback about daily practice use. Groot *et al.*[12] showed that the use of bortezomib in 2005 was almost three times higher in Sweden and France compared with the Netherlands. Furthermore, Dutch use in 2007 was a little less than 35 mg per 100,000 inhabitants while the European average (Austria, Belgium, Denmark, Finland, France, Germany, Italy, Netherlands, Norway, Spain, Sweden, Switzerland and the UK) was above 50 mg per 100,000 inhabitants.[13] Our results also showed that use was below HOVON's expected rate. Despite financial assistance, use and accessibility issues might thus still exist.

It remains subject to further research whether observed regional differences are due to physician prescription behaviour or referral to more experienced or wealthier hospitals. Differences seem to have decreased compared with previous outcomes of the trastuzumab study in 2005, which might be a result of the changes in the policy regulations. However, we should note that the trastuzumab study analysed patients with breast cancer, whose prevalence is much higher than multiple myeloma. Wagelaar *et al.* studied accessibility of two expensive drugs in the Netherlands, bortezomib and trastuzumab, mainly by investigating whether prescription was in accordance with guidelines at the individual patient

level.[22] Medical files were examined and interviews were conducted with physicians, members of hospital boards of directors, and patients. They concluded that guidelines were strictly followed and that recommendations by the professional association and patient characteristics determined treatment decisions. Although the budget of 80% was insufficient according to their respondents, accessibility was not an issue. Interestingly, while their results align with our interview results, they are in contrast with our quantitative findings and our research shows that differences in accessibility might not be revealed by using a qualitative research method only.

In 2012, changes in the regulations increased the additional earmarked budget to full coverage of the 'add-on' diagnoses-related group (i.e. 100% reimbursement of expensive drugs but hospitals and insurers negotiate on the price of the 'add-on'). Although hospital resources remain scarce, this might improve access and reduce remaining regional differences. It will be interesting to closely follow the consequences of this new policy.

We investigated equality in access to bortezomib in the context of Dutch policy regulations for expensive drugs. Use of bortezomib has increased over time although regional differences are still present. We obtained different conclusions using two methods. While interviews did not reveal absolute prescription barriers, regional differences and possibly underutilisation were observed by comparing sales data with incidence and prevalence data. It seems that appropriate drug use and thus also accessibility depends on various factors, regulatory and organisational characteristics of a healthcare system being two important ones. An evaluation of health policies should therefore be based on mixed methods and data triangulation. Such an evaluation provides insight and valuable feedback that can enhance evidence-based decision making for both healthcare providers and policymakers. This could improve appropriate drug use and ensure equal access to healthcare. In the end, efficient and equitable use of scarce resources increases society's benefits from a healthcare system.

Previous presentation

An abstract of the preliminary results was presented at the International Society for Pharmacoeconomics and Outcomes Research 2010, Value in Health Vol. 13, Issue 7, Page A471.

Conflict of interest statement

M. van Agthoven is employed at Janssen-Cilag, pharmaceutical companies of Johnson & Johnson. Janssen-Cilag had no role in the design of the study or interpretation of results. The remaining authors have nothing to disclose.

REFERENCES

1. Hutton J, Trueman P, Henshall C. Coverage with evidence development: an examination of conceptual and policy issues. Int J Technol Assess Healthcare. 2007;23:425-32.
2. Trueman P, Grainger DL, Downs KE. Coverage with Evidence Development: applications and issues. Int J Technol Assess Healthcare. 2010;26:79-85.
3. Borstkankervereniging. Report on treatment of breast cancer patients with metastatic HER2-positive tumors (Dutch: Rapport onderbehandeling van borstkankerpatiënten met uitgezaaide HER2-positieve tumoren). Utrecht, the Netherlands: Borstkankervereniging; 2005.
4. Delwel GO. Guidance for Outcomes Research for the assessment of the costeffectiveness of in-patient medicines. Diemen, the Netherlands: Healthcare Insurance Board. 2008.
5. Healthcare Insurance Board (College voor zorgverzekeringen). CFH-rapport 07/30 bortezomib (Velcade®). Diemen: College voor zorgverzekeringen; 2007.
6. Jagannath S, Barlogie B, Berenson J, et al. A phase 2 study of two doses of bortezomib in relapsed or refractory myeloma. Br J Haematol. 2004;127:165-72.
7. Richardson PG, Barlogie B, Berenson J, et al. A Phase 2 Study of Bortezomib in Relapsed, Refractory Myeloma. N Engl J Med. 2003;348:2609-17.
8. Richardson PG, Sonneveld P, Schuster MW, et al. Bortezomib or High-Dose Dexamethasone for Relapsed Multiple Myeloma. N Engl J Med. 2005;352:2487-98.
9. Kumar SK, Rajkumar SV, Dispenzieri A, et al. Improved survival in multiple myeloma and the impact of novel therapies. Blood. 2008;111:2516-20.
10. Verelst SGR, Blommestein HM, Karim-Kos HE, Huijgens PC, Sonneveld P. Trends in Incidence and Survival of Multiple Myeloma in the Netherlands in the Last Two Decades. Results From a National Population Based Study. Blood (ASH Annual Meeting Abstracts). 2011; 118: 5071.
11. Sonneveld P, Zweegman S, Vellenga E, et al. Guidelines for treatment of plasma cell dyscrasias in 2010. Ned Tijdschr Hematol. 2010;7:84-95.
12. Groot MT, Huijgens PC, Uyl-de Groot CA. Introduction of expensive pharmaceuticals in haemato-oncology in the Netherlands and throughout Europe. Eur J Hosp Pharm Pract. 2006;12:30-6.
13. Wilking N, Jönsson B, Högberg D. Comparator report on patient access to cancer drugs in Europe. Stockholm: Karolinska Instituet; 2009.
14. Cresswell JW. Research design: Qualitative, quantitative, and mixed method approaches. 2nd ed. California, United States of America: Sage Publication, Inc; 2003.
15. Netherlands Cancer Registry, http://www.iknl.nl.
16. Franken MG, Gaultney J, Blommestein HM, et al. Pilot outcomes research: Effects and costs of bortezomib in relapsed or refractory multiple myeloma. Diemen: College voor zorgverzekeringen; 2010, http://www.cvz.nl/binaries/content/documents/cvzinternet/nl/documenten/rubriek+zorgpakket/imta-onderzoek-dure-geneesmiddelen-1207.pdf
17. HOVON. HOVON 65 MM / GMMG HD4 Clinical picture: MM (Multiple Myeloom) ISRCTN64455289, http://www.hovon.nl/trials/trials-by-type/mm.html?action=showstudie&studie_id=5&categorie_id=3;.
18. HOVON. HOVON 86 MM Clinical picture: MM (Multiple Myeloom) EudraCT Number:2007-002533-37, http://www.hovon.nl/trials/trials-by-type/mm.html?action=showstudie&studie_id=60&categorie_id=3;.
19. GIP. GIP database, Health Insurance Board [in Dutch: College voor Zorgverzekeringen 2011, http://www.gipdatabank.nl/; 15-05-2012.
20. Rogers EM. Diffusion of Innovations. 4th ed. New York: The Free Press; 1995.
21. Berwick DM. Disseminating innovations in healthcare. JAMA. 2003;289:1969-75.
22. Wagelaar M, Lubberding S, Hugtenburg J, Wagner C. Accessibility of expensive drugs. An investigation into drug use in breast cancer and multiple myeloma. [in Dutch: Toegankelijkheid van dure geneesmiddelen. Een onderzoek naar geneesmiddelgebruik bij mammacarcinoom en multipel myeloom.]. Utrecht: EMGO+ Instituut en NIVEL; 2010.