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Experience with outcomes research into the real-world effectiveness of novel therapies in Dutch daily practice from the context of conditional reimbursement

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ABSTRACT

Policymakers more often request outcomes research for expensive therapies to help resolve uncertainty of their health benefits and budget impact at reimbursement. Given the limitations of observational data, we assessed its usefulness in evaluating clinical outcomes for bortezomib in advanced multiple myeloma patients. Data were retrospectively collected from patients included in the pivotal Assessment of Proteasome Inhibition for Extending Remissions trial (APEX; $n = 333$) and two groups of daily practice patients treated with bortezomib following progression from upfront therapy ($n = 201$): real-world patients treated as of May 2009 (RW-1; $n = 72$) and June 2012 (RW-2; $n = 129$). Prognosis, treatment, and effectiveness were compared. Outcomes research was useful for policymakers for addressing to whom and how bortezomib was administered in daily practice. It was limited however in generating robust evidence on real-world safety and effectiveness. The quality of real-world evidence on effectiveness was low due to missing data in patient charts, existing treatment variation and the dynamics in care during the novel drug's initial market uptake period. Policymakers requesting real-world evidence on clinical outcomes for reimbursement decisions should be aware of these limitations and advised to carefully consider beforehand the type of evidence that best addresses their needs for the re-assessment phase.

1. Introduction

Multiple myeloma (MM) is a malignant plasma cell disorder which accounts for 1% of all cancer diagnoses worldwide and 13% of all hematologic malignancies [1]. The survival of MM patients has improved substantially in the past decade partly due to the introduction of

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novel agents [2,3], among which includes bortezomib (Velcade®).

The pivotal phase III APEX (Assessment of Proteasome Inhibition for Extending Remissions) trial demonstrated superior efficacy of bortezomib compared to dexamethasone in advanced MM [4,5], leading to its approval in 2003 and 2004 by the FDA [6] and European Medicines Agency (EMA) [7], respectively. Policymakers were confronted with the challenge to balance early access with high uncertainty regarding bortezomib's effectiveness in daily practice and overall budget impact. To deal with such uncertainty, there is an increasing trend globally toward performance based reimbursement schemes. For bortezomib for example, the Netherlands instituted a coverage with evidence development scheme in 2006 for the indication of relapsed/refractory multiple myeloma [8,9]. This policy allows early access to an expensive novel drug, however, conditional on the obligation to perform outcomes research. Additional data from daily practice needs to be gathered on appropriate drug use (e.g., patient characteristics, types of treatments, dosages, and dose modifications), real-world effectiveness and actual costs in daily practice. A reassessment will determine whether or not the drug will continue to receive reimbursement.

Outcomes research does however have its limitations as it is based on observational data often collected during the diffusion phase of a new technology, lending it susceptible to bias [10]. Decision making that incorporates biased effectiveness data from daily practice could lead to the wrong decision and ultimately hinder rather than improve society's access to innovations in healthcare. Therefore, it is important to inform policymakers of the feasibility and usefulness of observational data to assess the therapeutic value of a new drug in daily practice.

To demonstrate the value of outcomes research in evaluating a drug's appropriate use and real-world effectiveness, we conducted an outcomes research study of bortezomib in advanced MM in the Netherlands following its EMA approval. We report here the evidence generated in daily practice compared to the trial and draw conclusions regarding the usefulness of observational data to assess the drug's therapeutic value.

2. Methods

Data on two patient cohorts receiving bortezomib for treatment of advanced MM were collected: one from daily practice patients treated in the Netherlands following progression/relapse or refractory disease from an RCT for upfront therapy ($n = 201$) [11], and one from the pivotal phase III APEX trial ($n = 333$) [4,5].

2.1. Patient groups

Information about the inclusion/exclusion criteria for each patient group is available in Table 1.

2.1.1. Daily practice patients

Daily practice patients were selected from 556 patients enrolled from November 2001 to June 2005 in the phase III Dutch-Belgian Cooperative Trial Group for Hematology Oncology (Stichting van Hemato-Oncologie voor Volwassenen Nederland) (HOVON)-50 trial [11] which investigated the treatment effect of thalidomide, adriamycin and dexamethasone (TAD) versus vincristine, adriamycin and

Table 1
Eligibility criteria applied for patient selection in daily practice versus the APEX trial.

	Trial setting ($n = 333$)	Daily practice ($n = 201$)	
	APEX ($n = 333$) [4,5]	RW-1 ($n = 72$)	RW-2 ($n = 129$)
Eligibility criteria For inclusion:	Measurable progressive disease after one to three previous treatments; Karnofsky ≥60; platelet count ≥50.000 per cubic millimeter; hemoglobin ≥7.5 g/dl; neutrophil count ≥750 per cubic millimeter; creatinine clearance ≥20 ml/min	Relapsed or refractory to HOVON 50 treatment protocol for first line; measurable progressive disease after one or more previous treatments; received bortezomib for relapsed/refractory disease in daily practice	Relapsed or refractory to HOVON 50 treatment protocol for first line Measurable progressive disease after one or more previous treatments Received bortezomib for relapsed/refractory disease in daily practice
For exclusion:	Previous bortezomib or refractory to high dose dexamethasone; Grade 2 peripheral neuropathy; any clinically significant coexisting illness unrelated to myeloma	Secondary malignancy (excluding basal cell carcinoma); received bortezomib for relapsed/refractory disease under a controlled trial setting	None
Study design	Randomized controlled trial	Retrospective observational design	Retrospective observational design
Data collection	Prospective	Detailed case reports using medical chart review performed by the authors	Data extracted from trial follow-up data collected by the HOVON Data Centre data managers
Date of follow-up	June 2002 to March 2006	January 2001 and May 2009 with date of last contacted updated as of June 2012	January 2001 and June 2012
Data points available for comparison	Baseline prognostic factors, treatment, adverse events, efficacy in terms of response rates, TTP and OS	Baseline prognostic factors, treatment, adverse events, effectiveness in terms of response rates, TTP and OS	Baseline prognostic factors and effectiveness in terms of response rates, TTP and OS

APEX: Assessment of Proteasome Inhibition for Extending Remissions; HOVON: Hemato-Oncologie voor Volwassenen Nederland; OS: overall survival; RW: real-world; TTP: time-to-progression.