

A Review of Patient-Reported Outcome Data for Palliative Cancer Drugs Approved In the European Union

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Received: January 28, 2018; Accepted: February 16, 2018; Published: February 22, 2018

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Abstract

Background: Results from patient reported outcome (PRO) are often undermined due to methodological issues thus limiting patient centeredness in clinical research for development of palliative cancer medicines.

Objective: The aim of this study was to identify the rate and type of PRO data included in the Summary of Product Characteristics (SmPC) for cancer palliative drugs approved in the European Union (EU) by December 21st 2017.

Results: From 115 approved cancer drugs, 6 or only 5.2% included PRO data in their SmPC about palliative cancer care, constituted by 4 international non-proprietary names (INNs) within 3 indications. Not all of them were used as a primary endpoint in the pivotal clinical trials.

Conclusion: The rate of PRO data included in the SmPC's of palliative cancer drugs approved in EU is very low and therefore all stakeholders should be encouraged to wider use of PRO tools in clinical research and development of palliative cancer medicines.

Keywords: Patient-reported outcomes; Cancer; Palliative drugs; Summary of product characteristics

Background

The Summary of Product Characteristics (SmPC) for medicinal products approved in the European union (EU) is the main public regulatory document, subject to approval by the regulatory authorities within the life cycle of a drug. The European Medicines agency (EMA) grants single marketing authorization for medicinal products in all 28 EU member states as well as to the 3 countries from the European Economy Area (EEA). Both the Food and Drug Administration (FDA) and EMA have guidelines on the use and interpretation of subjective measurement scales. In the EMA's guideline related to the use of PRO measures in oncology studies, PRO is defined as "any outcome evaluated directly by the patient himself or herself and is based on patient's perception of a disease and its treatment(s). PRO is an umbrella term covering both single dimension and multi-dimension measures of symptoms, HRQL, health status, adherence to treatment and satisfaction with treatment" [1]. A patient-

reported outcome (PRO) is defined by FDA as a "any report of the status of a patient's health condition that comes directly from the patient without interpretation of the patient's response by a clinician or anyone else" [2]. PROs are common tool for clinical evaluation of efficacy and quality of life in clinical research for chronic treatments such as palliative cancer care. PROs are also considered in Health Technology Assessment (HTA) models and included in the attributes of The HTA Core Model[®] (version 3.0) of the European network for HTA (EUnetHTA) - *integrating a European vision of the best HTA practice* [3]. Results from PROs however are often undermined due to methodological issues thus limiting patient centeredness in both clinical research and HTA. We hereby analyze PRO data included in the SmPC's of palliative cancer drugs approved by EMA.

Methods

All cancer drugs approved by EMA until December 21st 2017 were reviewed from the agency's website to check for indication/s eligible to be palliative based on the WHO definition for palliative care: "Palliative care is an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual". After excluding withdrawn, suspended or refused applications, search continued for medicines which are not biosimilars, generics and other drugs without pivotal trials as well as vaccines and imagine-related drugs. The relevant SmPC section was reviewed for data derived from PRO tools. In addition, information was collected about each PRO tool, PRO endpoint status in the studies and the design of pivotal clinical trials where PROs were included. Descriptive statistics were performed in Microsoft Excel[®] 2016.

Results

From 115 European Public Assessment Reports (EPAR) for cancer drugs available, 10 drugs included palliative indications (8.7%) and only 6 (5.2%) met the inclusion criteria, constituted

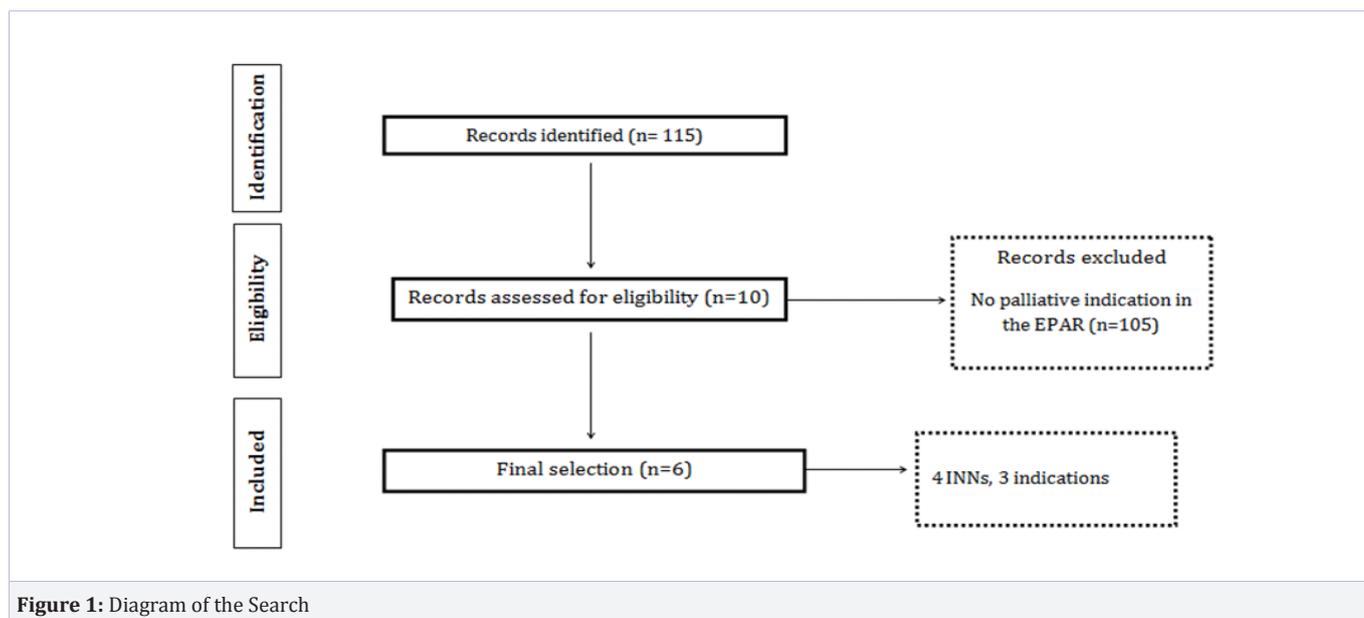


Figure 1: Diagram of the Search

Table 1: PRO data included in SmPC's for palliative cancer medicines approved by EMA

INN	Indication	PRO Tool	PRO Endpoint Status	Trial Design
Darbepoetin Alfa	Anemia cancer patients receiving chemotherapy	Fatigue scale /FACT/	Secondary	1 randomized, double-blind, placebo controlled trial
Fentanyl /as citrate/ Buccal tablets	Treatment of breakthrough pain /BTP/ for chronic cancer pain	Patient assessment of 11-point scale pain intensity /SPID60 and SPID 30/	Primary	2 randomized, double-blind, placebo-controlled, crossover trials.
Fentanyl /as citrate/ nasal spray solution	BTP for chronic cancer pain	SPID 30	Primary	1 randomized, double-blind, placebo-controlled crossover trial
Palonosetron /as hydrochloride/	Acute nausea and vomiting in emetogenic chemotherapy	Complete response (No Emesis and No Rescue) Complete Control (Complete Response no more than Mild Nausea) No Nausea (Likert scale)	Primary	3 randomized double- blind trials
Palonosetron /as hydrochloride/	Acute nausea and vomiting in emetogenic chemotherapy	Complete response (No Emesis and No Rescue) Complete Control (Complete Response no more than Mild Nausea) No Nausea (Likert scale)	Primary	3 randomized double- blind trials
Rolapitant	Nausea and Vomiting in emetogenic cancer chemotherapy	Functional Living Index-Emesis /FLIE/	Additional	1 randomized, double-blind, parallel group trial

by 4 international non-proprietary names (INNs) with granted in total 3 indications: anemia in cancer patients receiving chemotherapy /1 product/; treatment of breakthrough pain for chronic cancer pain /2 products/ and acute nausea and vomiting in emetogenic chemotherapy /3 products/ [Figure1].

All of them had 1 PRO tool, either from a single or from a composite method. For 4 drugs PRO was used as a primary endpoint in the pivotal trials, in 1 as a secondary and in 1 as additional endpoint / [Table 1].

Results from PROs used as primary endpoints were statistically significant. Where more than one drug were approved in the same therapeutic areas, PROs used were identical for chronic cancer pain and different in nausea/vomiting, while choice of PRO in this case was not justified. Another 4 drugs were approved for similar indications without PRO data and therefore not analyzed.

Discussion and Conclusions

Results reveal surprisingly low rate of approved palliative cancer drugs and a far too low rate of PRO data included in the SmPC's. Indeed, oncology products may not support PROs likely because of logistical hurdles and/or study design [4] but PRO use is more frequent in clinical trials of products for chronic, disabling conditions where the goal of treatment is not curing but rather an improvement in symptoms, functioning, or quality of life [5]. Low rate of PRO data in the main regulatory document – the SmPC in Europe – may well be one of the reasons why these important measures of patient satisfaction and cost-effectiveness are often under-used in daily practice [6, 7].

There may be different reasons for the low rate of PRO use in palliative care designated medicines. One of them is the low number of dedicated PRO instruments available and the lack of tools specific to the condition. This is a well-known problem in rare diseases and orphan drugs too [8]. It appears that typical health-related quality of life (HRQoL) methods are replaced with less complex tools –example with the five-point Likert scale to evaluate nausea compared to the validated 40-item quality of recovery (QoR-40) scale consisting clinically relevant dimensions [9]. Low rates of collection of PROs in pivotal clinical trials in palliative treatments are potentially underpinned by the lack of regulatory requirements that mandate the inclusion of PRO endpoints in drug development and validated methodologies. There is a need to increase use of PRO data in drug research for palliative cancer care. And there are incentives on the way. In EU calls for policy changes in HTA models are rising. Recent EU, WHO and others findings highlight inconsistency, variability and lack of predictability in the current HTA value frameworks urging authorities to encompass all attributes recommended by the EUnetHTA Core Model® where patient perspective, including PRO, should be considered[10-19].

There are a number of limitations in this analysis. The search inclusion and exclusion criteria were chosen subjectively and limited to least possible indications. As palliative care is not standard regulatory term some medicines may also be claimed to be eligible, i.e. drugs for prevention of bone fractures in cancer

patients. Finally, the results of this analysis are not generalizable to cancer drugs other than the listed with a similar regulatory profile as described herein.

In conclusion, the rate of PRO data included in the SmPC's of palliative drugs approved in EU/EEA is very low. There is a need to encourage all stakeholders for wider use of PRO tools in both clinical research and HTA as patient centeredness in this therapeutic area is especially challenging and sensitive.

Compliance with Ethical Standards

Authors declare that no funding was received to conduct the research presented here.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

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