Journal of Cancer Policy xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Journal of Cancer Policy

journal homepage: www.elsevier.com/locate/jcpo

Reviews

Rare cancers—Rarity as a cost and value argument

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ARTICLE INFO

Article history:
Received 9 April 2016
Accepted 5 September 2016
Available online xxx

Keywords:
Rare diseases
Cancer
Health care systems
Cost

ABSTRACT

Here is a paradox in medicine: rare diseases are unusual, but developing a rare disease is quite frequent. This is also true for rare forms of cancer. Almost every 20th person in the world suffers from a rare disease, and about one quarter of all new diagnosed cancers belong to rare cancers. The downside of rare diseases for patients is the difficulty to find the right institution for their treatment, for health care payers it is the costly treatments, and for medical professionals their limited knowledge if they are not specialized in the disease in question. On the other hand, the upside for clinical researchers is that rare diseases are beneficial for their scientific careers, as many clinical and scientific questions are still open. The advantages for the pharmaceutical industry are the premium prices, the special governmental programs to stimulate research, and achieving a dominant position in a small market. To sum up, rare cancers are important for all stakeholders in medical care and deserve more attention from public health research.

Contents

1. Rare diseases are quite frequent

About 7000–8000 of the 30,000 known diseases are rare diseases, also commonly known as orphan diseases [1]. The European Union (EU) defines a rare disease as having a prevalence of less than 500 cases per million people [2]. In contrast, rare diseases in other countries are defined through different prevalence rates: e.g., in United States (US) 750, in Japan 400, and in Australia 120 patients per million people [3].

It seems paradoxical that, while the patient population for each rare condition is small, the aggregate population of people living with a rare disease is large. Moreover, many people living with a rare disease do not know that they are ill, or they search unsuccessfully for a diagnosis or therapy. The prevalence of all rare diseases is approximately 5%, with about 400 million rare disease patients worldwide. In the EU, 27–36 million people suffer from rare diseases. In the US, where there are approximately 25 million citizens with rare diseases, the estimated prevalence is similar to that in the EU [4]. In Germany alone, approximately 4 million patients suffer from a rare disease [5]. This generates a paradox of rarity: suffering from a rare disease is actually quite common.

One of the most common and well-known rare diseases is cystic fibrosis (CF) or mucoviscidosis. CF has a prevalence of 500 in a million in Europe and is a complex lifelong chronic disease caused by genetic mutations. Like in CF, in 80% of rare diseases, a gene defect causes the condition. In most cases, CF affects multiple organ systems. The average life expectancy for patients with CF has increased from only a few months in the 1950s to 30–50 years nowadays. In Germany, there are about 8000 patients living with diagnosed CF. In contrast to CF, ribose-5-phosphate isomerase deficiency is

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http://dx.doi.org/10.1016/j.jcpo.2016.09.004
2213-5383/

the rarest disease in the world, with only one known case. Therefore, researchers need to be cautious when formulating general statements on rare diseases.

Clinical research has developed very effective treatments for many rare diseases in recent years. However, many of these are quite costly. For instance, the lifetime costs of treating a patient with type 1 Gaucher's disease in a Dutch setting is 5,716,473 Euro [6]. For many other diseases, a symptomatic or no treatment is available.

In contrast to rare diseases in general, the definition of rare cancers is based on incidence instead of prevalence because prevalence can be a misleading indicator of rarity for disorders that occur infrequently. In the EU, cancers are commonly classed as rare when they have an incidence of ≤60 per million people per year [7]. However, the US National Cancer Institute defines rare cancers as having an incidence rate of 150 per million people per year. About 22–27% of all diagnosed cancers are rare (22% of all annual cancer diagnosis in the EU [7]), and they cause about one quarter of all deaths by cancer [8–10]. Similar to rare diseases in general, it is useful to distinguish between "frequent rare cancers" such as stomach, head, and neck cancer and "rare rare cancers" such as eye cancer. Clinical research has developed individualized medical concepts to treat rare carcinoids. However, these concepts lead to high, and in some cases very high, treatment costs for patients. Moreover, personalized medicine and increasingly sophisticated molecular pathology lead to new challenges for developing and price setting of orphan products.

In this paper, we discuss the public health and economic challenges posed by rare diseases. We also draw attention to the specific challenges that rare forms of cancer present for health care systems and clinical and public health research, and in particular the assessment of value for innovative treatments for rare cancers, and the role of precision medicine and targeted therapies.

2. Rare diseases from an economic point of view

In the well-known article "The Voluntary Exchange Theory of Public Economy" [11], published in 1939 by Richard Musgrave, the responsibilities of a government are structured into three major "branches": the stabilization of the economy, (re)distribution, and achievement of an efficient allocation of resources. This conceptual division of the responsibilities of governments can also be transferred to health care systems. From an economic viewpoint, we can identify three major tasks for health care systems. Firstly, high-quality health care has to be provided consistently and appropriately to all patients in a country (stabilization). Consequently, people should not face disadvantages in the health care system because of the rarity of their diseases; more precisely, all patients should have equal access to health care facilities. The system should prioritize those who have the largest needs, and accordingly, the financing scheme of the health care system should pursue society's equity values (distribution). Health services should function effectively, and the health care system should use the scarce resources efficiently in order to maximize the wellbeing of patients (allocation). These are precisely the economic challenges of health policy in all countries, and they apply to the treatment of rare diseases in particular.

3. Challenges for the health care system posed by rare diseases in general

Rare diseases pose a number of challenges for health care systems. From a dual economic and organizational point of view, the following six issues can be formulated:

1. In many cases, the diagnosis of rare diseases is very difficult due to their rarity and heterogeneity. The majority of physicians have little or no experience with these disorders, e.g. rare childhood or rare eye cancer. Educational efforts and better information systems can help both physicians be more sensitive towards rare diseases and patients to reduce their time-consuming odyssey through the health care system. Patients often get neither the correct treatment nor a name for their illness. An accelerated and improved diagnosis through the use of novel diagnostic technologies based on genome sequencing methods could reduce health-related suffering and the underuse and misuse of health care resources. However, at this time, genome sequencing is very costly.
2. Because the number of rare disease patients is small, the question is how to organize appropriate care for these patients. Specifically, the health care system needs to create specialized outpatient care units. These centers should have close contact with medical universities to incorporate the recent innovations into the treatment of patients with rare diseases.
3. The distribution of specialized centers has to be decided by health care payers. They should consider whether the implementation of a few centers in each country or large region, or even only one center, is more suitable to serve rare disease patients. The EU has developed criteria to establish European Reference Networks (ERN) for rare diseases. The legal framework for creating a system of ERN was established with EU Article 12 of Directive 2011/24/EU [12]. To ensure the efficiency of health systems and access to high-quality health care, these networks should be able to collaborate, coordinate, and share their knowledge across borders. However, up to now, evidence regarding the efficiency and validation of organization models for complex networks such as ERN is missing. Furthermore, cross-border financing for ERN is challenging.
4. In many cases, the treatment of rare diseases is extremely costly. The cost of orphan drugs alone absorbs a significant and growing part of health care budgets due to the increasing number of declared orphan drugs with high prices. The budget impact of orphan drugs in Sweden and France was analyzed by British researchers using a dynamic forecasting model [13]. In 2013, orphan drugs amounted to 2.7% of the total drug expenditures in Sweden and 3.2% in France. By 2020, these costs are expected to reach 4.1% in Sweden and 4.9% in France [13]. Society in general and health care payers in particular need to decide how much they are willing to pay for the treatment of rare diseases. A macroeconomic allocation dilemma has resulted from having limited resources: if society's spending on the treatment of rare diseases increases, the resources for the treatment of more common diseases need to decrease.
5. Without special regulations and incentives, pharmaceutical companies will spend less money on the research and development of drugs used in the treatment of patients with rare diseases. This is due to the small market for these highly specialized drugs, given the low number of patients in comparison to broader indications, such as asthma, chronic obstructive pulmonary disease (COPD), diabetes, hypertension, coronary heart disease (CHD), depression, and dementia [14]. National and supra-national organizations have imposed incentive schemes to stimulate research on the treatment of rare diseases. Since 2003, the European Commission, for instance, has approved 111 drugs as orphan drugs (including 6 anti-cancer drugs) in the EU [15]. These drugs go through a facilitated registration process. In general, after the licensing of a new drug, a health care payers' organization or a public institution decide on its pricing and reimbursement. This "fourth hurdle" has been imposed by many countries in the last years (Australia in 1987, Canada in 1994, and England in 1999). In 2011, Germany introduced its fourth

Please cite this article in press as: J.-M. Graf von der Schulenburg, F. Pauer, Rare cancers—Rarity as a cost and value argument, J Cancer Policy (2016), http://dx.doi.org/10.1016/j.jcpo.2016.09.004