Health economics of targeted cancer therapies
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Aging population in Serbia

Serbia is a country located in the central part of the Balkan Peninsula, commonly referred to as the South Eastern Europe. According to the last census held in 2011 Serbia had 7.2 million citizens\(^1\). Some of recent demographic characteristics of Serbia are the negative natural increase rate, significant emigration and abrupt aging. Firstly, the annual balance between number of new-borns and number of deaths was negative at around 37,000 people (-5.2‰) and since the 1991 census it has been constantly below zero [3,4]. This was caused by a low and steadily decreasing fertility rate. Secondly, the net migration, the difference between number of people emigrating from the country and those immigrating into the country, has also been negative [5,6]. Consequently, population aging has become an important concern for Serbian healthcare policy making the current median age in Serbia 42.2 years, which is the third oldest median age recorded in Europe and it can be regarded as one of the oldest in the world [1,7-9]. At least until the mid-21\(^{st}\) century, Serbian population will continue to contract, with the latest estimates predicting just above 5 million people in 2061 [4]. By the same year the proportion of people older than 65 will nearly double and reflect one third of the population.

Population aging is the main impetus for ever increasing incidence and mortality of cancer worldwide [10]. The estimated number of newly diagnosed cancer patients on the planet is predicted to raise from 14 million in 2012 to 22 million in 2030, and proportions of patients older than 65 will constitute more than half of the latter estimate [11]. Cancer recently became the second leading cause of death globally and its monitoring is an essential prerequisite for the preparation of appropriate and rational oncologic care [11,12]. With rapid population aging, Serbia is presented with the problem of providing effective cancer care for an increasing cancer population which at the same time will be affordable for such a mid-income country. The science of Health Economics and the economic evaluation and health technology assessment methods could provide answers as to how such goal can be achieved.

Cancer epidemiology in Serbia

Completeness and quality of data on cancer epidemiology in Serbia have been improved over the years [13]. From their formation, two local cancer registries collected data separately: the Cancer Registry of Central Serbia (CRCS; 74% of total population)\(^2\) [13] and the Cancer Registry of Vojvodina (CRV; 26% of total population)\(^3\) [unpublished data – Miladinov-Mikov]. Nonetheless, prior to the research shown in this thesis, data were never published on the national level. Therefore, world databases such as GLOBOCAN, and available publications on cancer epidemiology in Serbia would rely on one of the local registries, or only on mortality data from the Statistical Office [15,18]. Some reports have focused only on specific cancer sites, outdated data or narrowed time frames [15-20].

Data from the CRCS indicate that the most frequent and more deadly cancers in men are lung, colorectal and prostate cancer, whereas in women breast, cervical and colorectal cancer are the most frequent [15]. Combined data from both the CRCS and CRV reveal that there were around 36,000 new cancer cases and 21,000 cancer deaths in Serbia in

\(^{1}\) Demographic and epidemiologic data for Serbia presented within this thesis does not contain data for the Autonomous Province of Kosovo and Metohija (KiM). Although Serbia does not govern this territory as of 1999, KiM is not recognised as an independent state by the United Nations. Population of KiM is estimated at 1.8 million and there are no official data on cancer epidemiology to this date [2].
Chapter 1

2009 [13, unpublished data – Miladinov-Mikov]. The comparison with other countries or analysis of trends is possible only after age standardisation of CRCS and CRV data and involving their long term follow up. Some comparisons of individual cancer sites identified standardised cervical cancer incidence and mortality rates in Serbia as one of the highest in Europe [19,20]. Furthermore, years lost due to cancer in Serbia were estimated to be higher than the European average for colorectal and lung cancers in both genders and breast cancer in women [17]. Better understanding of cancer epidemiology in Serbia and identification of risk factors is important for successful organisation of oncologic care and adequate design of preventive and therapeutic strategies, inclusive cost-effectiveness.

Economy and health care system

According to the Human Development Index - a composite proxy measure of life expectancy, population’s education and income - Serbia ranks 77th among 187 countries [21]. Although it is classified as an upper-middle-income economy by the World Bank, with the gross domestic product (GDP) of around €4,500 per capita, Serbia is one of the poorest countries on the European continent [22,23]. For two and a half decades Serbia is transiting its economic system from a former socialistic government-centred society to an open market economy. The process was firstly hampered by the wars and economic sanctions (1991-1999) and later by the world finance crisis (2008) [24]. Essentially, the only period of stable economic growth happened between these two events when GDP nearly doubled from €2,600 to €4,600 per capita [25]. This course of transition was mirrored in the financing and organisation of the health care system.

The public health care system in Serbia is financed mainly through the obligatory insurance paid by all employees while benefits are received practically by whole population [26]. The National Health Insurance Fund (srb. Republički fond za zdravstveno osiguranje – RFZO) is in charge of managing compulsory insurance, provided through state-owned facilities. It is estimated that RFZO covers around 65% of total health care expenditures , with the rest incurring in private clinics, paid directly by patients or indirectly through private funds [27]. Transition to this model of financing happened in as much as 22 out of 28 former socialistic countries with the main motivation to separate funding stream for healthcare from the state budget [28]. Ideally, this transition enables healthcare to be better available to the citizens. However, the pitfall of the model is obviously inadequate funding in countries with low employment rates and insufficient financial discipline. For example, too low revenues from insurance payment led to a considerable debt of the RFZO (€1 billion) to healthcare providers which threatened to paralyse the whole drug supply system in 2012. The debt was partly transferred to public debt and stricter control was installed in order to recover the healthcare sector [29].

To understand the issue with financing, one should know that planned annual expenditure for the RFZO is €1.8 billion or around €250 per capita [23,30]. Half of this sum covers the expenses for secondary and tertiary healthcare services (specialists’ care), and around 20% goes to the primary healthcare services (general practitioners, paediatricians and gynaecologists) [30]. Total drug expenditure per capita is €70 (28% of healthcare expenditure), divided between hospital drugs (16%) and prescribed drugs (12%) [30]. Despite being relatively small, drug expenditure of the RFZO increased 2.18 times in the period from 2004 to 2012, following the described increase of GDP at the time. Yet, increase in the expenditures on oncologic drugs of 4.97 times in the same period was disproportionally high [31].
Reimbursement policy for drugs in Serbia has been defined by the RFZO Rule Book [32]. The document defines internal RFZO committees that will inspect the additional clinical value, as well as the pharmacoeconomic value of a new drug. Pharmacoeconomics is assessed through an obligatory cost utility analysis (CUA) for any drug with a new generic name, together with a budget impact analysis (BIA). Except from the basic definitions of the CUA and BIA, the RFZO Rule Book does not specify any details on how the analyses should be conducted or what would be guidelines and decision criteria. Additionally, none of the submission and revision documents become publically available during the application process. The final decision is issued through the five reimbursement lists (A, A1, B, C, D), which mainly differ in dispensability, level of patients’ co-payment and potential prescription restrictions [33].

**Targeted cancer therapies and their pharmacoeconomics**

Targeted cancer therapies (TCTs) are drugs that act on predefined molecular pathways specific for a cancer cell causing its regression and/or destruction [34]. Their selectiveness for a target molecule should result in higher effectiveness and a better safety profile in comparison with standard chemotherapy. Therefore, identifying molecular targets followed by synthesis of corresponding TCTs’ emerged as one of the main concepts in the development of new cancer drugs.

Since the market authorisation of the first TCT in late nineties [35], this therapeutic group experienced rapid expansion. For example, the number of licensed TCTs in 2010 was 22, while already in 2014 there were 41 registered TCTs by European Medicines Agency (EMA) and/or US Food and Drug Administration (FDA) [36-38]. In terms of revenues, these drugs present the largest and fastest growing part of oncological therapeutics, the most dominant therapeutic group in the global pharmaceutical market [36,39].

Clinical efficacy of TCTs has been observed over on survival and/or quality of life across different cancer types, but also came at a considerable cost [40]. Different assessments and reimbursement policies applied to address this issue resulted in significant differences in TCTs’ access between European countries. Pharmacoeconomic analysis in particular proved to be one of the most decisive elements within the assessments of TCTs [41,42].

A challenging part in pharmacoeconomic assessment of TCTs is an accurate estimate of their effectiveness. Summary survival data reported in randomised clinical trials (RCTs) which compare a treatment of interest with the current standard of care, are frequently the only publically available source for the drugs’ effectiveness. Data on two outcomes, overall and progression-free survival (OS and PFS) are presented graphically through Kaplan Meier curves, potentially followed by the number of patients at risk at certain time points and treatment effects described by an estimate of hazard ratio. Additionally, trials can encompass insufficient number of patients, can have limiting follow up periods, or allow the cross over from the control treatment to the TCT. On the other hand, proper health economic assessment should be based on lifelong treatment effects, include all relevant treatment options, and should be extensive to the total target population within a health care system.

Numerous methodological issues in estimate survival data in economic evaluations are flagged in the literature [43,44]. Even the most prevalent way of modelling survival from RCTs which relies on the parametrisation of the Kaplan Meier curve for baseline treatment and application of estimated hazard ratio has some apparent flaws in its underlying
assumptions [44,45]. Inclusion of several RCTs in the network of evidence for survival analysis with the aim of simultaneous comparison of all relevant treatment options brings additional modelling issues [44,46]. Careful consideration of all taken assumptions and testing of their appropriateness is therefore a requirement in a TCTs survival analysis.

**Aims of the thesis**

The general aim of this thesis is to provide an overall picture on the cost effectiveness of the TCTs in the epidemiological, clinical and economic conditions of Serbia, with comparisons to the Dutch situation where possible. Prerequisites for this research are understanding of trends in cancer epidemiology and identification of costs and clinical pathways in the oncologic care within the country. Since official Serbian data on these inputs were scarce, basic investigation to obtain epidemiological estimates and describe present clinical practice algorithms was firstly conducted. Secondly, cost effectiveness of TCTs was examined in the field of metastatic renal cell cancer (mRCC). The mRCC is chosen, as it has typical characteristics of a TCT indication with multiple comparators being present both at first and second line of treatment. Parallel to the pharmacoeconomic outcomes of TCTs in Serbia, this research analyses similar issues in a Dutch context which vary with respect to different economic and clinical factors. Thirdly, in order to test increasing numbers of TCTs which present the same active substances of identical effectiveness available in different pharmaceutical formulations (e.g. trastuzumab in breast cancer and rituximab in Non-Hodgkin Lymphoma), cost minimisation and budget impact analyses are employed. Finally, based on its original findings, this thesis tries to offer practical recommendations to the Serbian health authorities on how to construct rational and sustainable policies in TCTs assessment and reimbursement.

The thesis is structured in three parts. **Part I** considers the general conditions in which TCTs are analyzed, such as epidemiology of cancer in Serbia and public access to the TCTs in the country. Therefore, **Chapter 2** systematically presents incidence and mortality of 10 most frequent and most fatal cancers on national levels in the period 1999-2009. Comparison of age standardised rates within the European regions is conducted using GLOBOCAN database estimates. For comparative purposes, **Chapter 3** discusses current accessibility to TCTs in Serbia, Netherlands and Scotland and analyses differences in their reimbursement policies with regards to different health economics applications. Comprehensive lists of all FDA and/or EMA authorised TCTs with their reimbursement statuses in the respective countries is presented.

In **Part II**, cost-effectiveness is evaluated within the field of mRCC. Firstly, an example of one drug CUA and BIA utilising a standard area-under-the-curve Markov model is given with everolimus as a second line therapy in **Chapter 4**. State-of-the-art fractional polynomial network-meta analysis is used in **Chapter 5** to assess effectiveness of all clinically proven first line TCTs in mRCC. This method was additionally compared to the standard parametric approach based on hazards proportionality and differences in the outcomes were analysed. The relative survival estimates obtained in Chapter 5 are consequently used to inform a cost effectiveness analysis of first line mRCC treatments for both Serbia and the Netherlands.

**Part III** relates to the examination of equally effective TCTs with different routes of administration. Notably, some TCTs become available in two different pharmaceutical formulations, e.g. newer subcutaneous forms substitute earlier intravenous and claim to bring in cost savings when compared to the earlier formulations. For this purpose two
cost minimisation models, dependent on data availability, are applied in Serbia and the Netherlands. In Chapter 6, costs of subcutaneous trastuzumab are compared to those of intravenous trastuzumab with regard to their use in HER-2 positive breast cancer patients in Serbia. In Chapter 7, costs of subcutaneous rituximab are compared with those of intravenous rituximab in Non-Hodgkin Lymphoma within the Dutch setting. In two practical and detailed cost analyses differences in costs between two quite distinctive health care systems are explained.

Chapter 8 finalizes the thesis with general discussion and recommendations.

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PART I:

EPIDEMIOLOGY OF CANCER AND ACCESS TO TARGETED CANCER THERAPIES IN SERBIA