Health economics of targeted cancer therapies
Mihajlovic, Jovan

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CHAPTER 3

REIMBURSEMENT OF TARGETED CANCER THERAPIES WITHIN THREE DIFFERENT EUROPEAN HEALTH CARE SYSTEMS

Mihajlović J, Dolk C, Tolley K, Simoens S, Postma MJ
Abstract

Purpose: Targeted cancer therapies (TCTs) are drugs that specifically act on molecular targets within the cancer cell causing its regression and/or destruction. They bring clinically important gains in survival in one of the most challenging therapeutic areas, yet, this is followed by considerable increase in healthcare expenditures. The aim of the present work was to identify differences in the recommendations for TCTs in three distinctive European healthcare systems: the Serbian, Scottish and Dutch, and to examine the role of pharmacoeconomic (PE) assessment in such recommendations.

Methods: A list of currently approved TCTs cited from the European Medicines Agency (EMA) was cross-referenced with the drug reimbursement reports issued by National Health Insurance Fund (RFZO) for Serbia, Scottish Medicines Consortium (SMC) for Scotland and National Health Institute (ZiNL) for the Netherlands. The following key variables were gathered from the reports: drug indication, registration status, reimbursement status and outcome of the PE evaluation.

Findings: There were 41 TCTs approved for 70 cancer indications by EMA. Out of total number of TCTs' indications (TCT/i), 20 were reimbursed in Serbia, and 25 are still without the decision from RFZO. Remaining TCT/is (25) are not registered in Serbia. None of submissions neither PE analyses were publically available. Scottish SMC positively assessed 26 TCT/i and rejected as much as 30 TCT/i. All appraisals were published, and majority contained full PE assessments. Finally, Dutch ZiNL accepted total of 60 TCT/i and disapproved use of only 1 TCT/i. The majority of reimbursed drugs were exempted from PE evaluation in accordance with two recent policies for expensive hospital drugs.

Implications: Reimbursement statuses of TCTs significantly differ in three examined healthcare systems. Level of PE application within TCTs' evaluation procedures seem to largely affect final reimbursement decisions. While in the Netherlands there are special policies which enabled fast access for 98% of TCTs that applied for reimbursement, clear definition of cost effectiveness threshold and strict requirement for full cost utility assessment in Scotland led to acceptance of only 46% of TCTs' submissions. More precise pharmacoeconomic guidelines are still to be designed for reimbursement of cancer pharmaceuticals in Serbia. Guidelines must account for specific epidemic and economic conditions of the country and could build on the experiences of Scotland and the Netherlands.
Introduction

Targeted cancer therapies (TCT) are drugs that interfere with specific predefined molecular targets involved in cancer cell growth and survival. It is necessary, however, that these targets are clearly identified, either quantitatively or qualitatively, and there is a correlation between their presence and an estimate TCT relative effectiveness [1]. Selectiveness for processes within cancer cells is what makes a distinction between TCTs and traditional chemotherapies. This selectiveness provides TCTs the potential for improved effectiveness associated with less severe adverse events than conventional chemotherapy regimens.

Dozens of TCTs were licensed worldwide since the first market authorisation of rituximab that took place in late nineties [2]. The total number of TCTs in 2010 was 22, while only four years later there are 44 registered targeted therapies for oncological indications issued by European Medicines Agency (EMA) and/or US Food and Drug Administration (FDA)[3-5]. By revenue, these drugs comprise the biggest and fastest growing part of oncological therapeutics which present the most dominant therapeutic group at the global pharmaceutical market [3,6].

Although TCTs showed clinically important gains in survival and/or quality of life within the indications that did not see any improvements in past, they also came at considerable cost [7]. Different policies in drugs' pricing and reimbursement among European countries that were applied to address this issue resulted in significant imbalances in TCTs’ access. Many countries developed health technology assessments’ processes to appropriately value all clinical and economic aspects of new oncological drugs. Economic evaluation appeared to be an influential element in these assessments [8]. In order to illustrate the variety of approaches and its effect on TCTs’ reimbursement we chose to examine three distinctive health care systems in Europe: the Serbian, Scottish and Dutch.

The main principles behind the reimbursement of pharmaceuticals in Serbia have been defined within the Rule book issued by the Government and applied in practice by the National Health Insurance Fund (in Serbian: Republički fond za zdravstveno osiguranje - RFZO) [9]. Together with the common requests for clinical efficacy, this regulation demands the CUA and budget impact analysis (BIA) within submission procedure for any new medicine. However, except from basic definitions of the CUA and BIA, more details of what should they include or specification of a cost effectiveness threshold were not provided. The assessment is performed by the RFZO committees and all drugs that gain positive decision can be placed at the five reimbursement lists which mostly differ in dispensability, level of patients’ co-payment and potential prescription restrictions. Furthermore, the RFZO does not consider TCTs, or any other therapeutic group separately from the general policy. Decisions are made publically available through the reimbursement lists [10], yet, they do not contain submission files or respective evaluations.

In Scotland, drug assessments are performed by the Scottish Medicines Consortium (SMC), a committee that advises local boards of the National Health Service (NHS) on the use and reimbursement of newly licensed drugs [11]. A standard SMC assessment examines a drug’s clinical efficacy and cost effectiveness and can engage the manufacturer, clinical experts and patients’ groups within the process. Consequently, detailed reports are produced and published at the SMC site. A drug is generally considered cost effective if its incremental cost effectiveness ratio (ICER) falls below £20,000 per quality-adjusted life-year (QALY) and not cost effective if the ratio is over the threshold of £30,000/QALY.
Drugs with the ICER between two cited values can be regarded as cost effective if they bring significant benefit when compared to the standard treatment. Although there are no exemptions from the regular procedure for a particular therapeutic group or patients’ population, the SMC recognises certain decision modifiers that can enable a positive recommendation despite relatively high and otherwise unacceptable cost effectiveness ratios. Decision modifiers potentially ascribed to TCTs are: substantial improvement in the survival or quality of life, absence of any therapeutic alternative and additional benefit for specific patients’ subgroups.

Finally, in the Netherlands, the National Health Institute (in Dutch: “Zorginstituut Nederland” – ZINL; formerly known as “College voor Zorgverzekeringen”- CvZ) conducts assessments of manufacturer submissions files on drugs and suggests their reimbursement status to the Ministry of Health, that generally follows the advice. In deciding on a manufacturer’s submission CvZ/ZINL evaluates a drug’s clinical value, cost effectiveness and budget impact. Although a cost effectiveness threshold is not predetermined, pharmacoeconomic assessment can influence the final reimbursement decision. Additionally to the general reimbursement procedure, there are two recent policies with several updated versions that may be applied to TCTs’ reimbursement. As of 2002, the Policy Rule for Expensive Hospital and Orphan Drugs (PREHO) supports supplemental financing of hospitals for use of expensive and orphan drugs. The regulation that replaced it from January 2012, and that is currently active, allows fast access to an even broader group of medicines. More precisely, the updated fast access PREHO (UFAP) is intended for conditional reimbursement of clinically effective hospital drugs with yearly drug cost per patient of more than €10,000 and total budget impact of more than €2.5 million. In 2015, the limit of €10,000 within the current policy will be removed, thus allowing even cheaper hospital drugs to be considered through the UFAP. Drugs that the PREHO and UFAP policies refer to were guaranteed fast access only after proving the additional clinical value, and cost effectiveness evaluation could have been averted initially. However, this kind of reimbursement is considered only temporary (conditional reimbursement), and reassessment is obligatory to start within four years after initial approval and inclusion of the real-world economic and clinical data for full pharmacoeconomic assessment.

The aim of the present work is to identify differences in the reimbursement statuses of TCTs in three European healthcare systems, i.e., the Serbian, Scottish and Dutch. In particular, we examine the role of pharmacoeconomic (PE) evaluation within the assessment procedures and its impact on the reimbursement statuses. The study also provides illustrative examples of distinctive healthcare policies and their relation to TCTs’ market access.

**Methods**

In order to introduce main characteristics of respective healthcare systems, we firstly present a number of structural parameters for Serbia, Scotland and the Netherlands. These include: population (total number, annual growth and age structure), cancer epidemiology (absolute annual number of new cancer cases and deaths, ratio of cancer deaths and new cancer cases) and basic healthcare funding parameters (total gross domestic product [GDP], GDP per capita, total healthcare expenditure, healthcare expenditure per capita and predominant source of health care funding). Official statistical data of Serbian, Scottish and Dutch government were cited. All parameters were taken for the latest available years, with an exception of population figures that were all set to the same year, 2013.
Secondly, a list of currently approved TCTs and therapeutic indications was formed from the available databases of the EMA [24]. New oncologic drugs that do not explicitly comply with the concept of TCTs, such as new hormonal oncologic therapies (e.g. abirateron acetate) or new chemotherapies (e.g. cabazitaxel, pemetrexed), were not included in the list. The same TCT could have been registered for more than one indication. The list of TCTs and approved therapeutic indications was then cross-referenced with the drug reimbursement lists and reports issued by the RFZO for Serbia, the SMC for Scotland and the CvZ/ZiNL for the Netherlands as of 15th of August 2014 [9,10,14]. The following variables were gathered from cited sources: reimbursement status, type of PE assessment and outcomes of such an assessment if available in terms of ICERs or cost per patient. As for the Netherlands, due to the temporal effect of a granted reimbursement status, which is frequently conditional and requires reassessment in the future, we included additional sources from CvZ/ZiN [25] to differ between reimbursed TCTs that need reassessment and TCTs that do not need reassessment in the future.

**Results**

Table 1 presents population, cancer epidemiology and healthcare funding parameters in Serbia, Scotland and the Netherlands. It is noted that the Serbian population is the only with negative annual growth (-4.8‰) and the relatively highest proportion of population above the age 65 (17.3%). Furthermore, the ratio of annual cancer deaths and cancer cases is the highest in Serbia (0.58), followed by the Netherlands (0.43) and Scotland (0.38). As far as the economies are concerned, Scottish and Dutch economies are producing comparable GDP/capita (€32,443 and €38,315 respectively), while GDP/capita in Serbia is much lower at €4,464. Correspondingly, investments in healthcare are €3,095, €2,387 and €282 per capita for the Netherlands, Scotland and Serbia, respectively.

Table 1: Population, cancer epidemiology and health care funding parameters in Serbia, Scotland and the Netherlands

<table>
<thead>
<tr>
<th></th>
<th>Serbia</th>
<th>Scotland</th>
<th>The Netherlands</th>
<th>Sources</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total population:</td>
<td>7,164,132</td>
<td>5,327,700</td>
<td>16,778,025</td>
<td>[18,20,22]</td>
</tr>
<tr>
<td>Annual population growth:</td>
<td>-4.8‰</td>
<td>2.7‰</td>
<td>2.8‰</td>
<td>[18,20,22]</td>
</tr>
<tr>
<td>Proportion of population aged 0-14:</td>
<td>14.40%</td>
<td>16.10%</td>
<td>17.00%</td>
<td>[18,20,22]</td>
</tr>
<tr>
<td>Proportion of population aged 15-64:</td>
<td>68.30%</td>
<td>67.20%</td>
<td>67.40%</td>
<td>[18,20,22]</td>
</tr>
<tr>
<td>Proportion of population aged &gt;65:</td>
<td>17.30%</td>
<td>16.70%</td>
<td>15.60%</td>
<td>[18,20,22]</td>
</tr>
<tr>
<td><strong>Cancer epidemiology</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Annual number of registered cancer cases:</td>
<td>36,308</td>
<td>41,322</td>
<td>101,210</td>
<td>[19,20,23]</td>
</tr>
<tr>
<td>Annual number of cancer deaths:</td>
<td>21,069</td>
<td>15,864</td>
<td>43,666</td>
<td>[19,20,23]</td>
</tr>
<tr>
<td>Ratio cancer deaths / new cancer cases</td>
<td>0.58</td>
<td>0.38</td>
<td>0.43</td>
<td>[19,20,23]</td>
</tr>
<tr>
<td><strong>Healthcare funding</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gross domestic product (in million):</td>
<td>€ 31,980</td>
<td>€ 172,849</td>
<td>€ 642,851</td>
<td>[18,21,22]</td>
</tr>
<tr>
<td>Gross domestic product per capita:</td>
<td>€ 4,464</td>
<td>€ 32,443</td>
<td>€ 38,315</td>
<td>[18,21,22]</td>
</tr>
<tr>
<td>Total healthcare expenditure (in million):</td>
<td>€ 2,018</td>
<td>€ 12,720</td>
<td>€ 51,926</td>
<td>[18,21,22]</td>
</tr>
<tr>
<td>Healthcare expenditure per capita:</td>
<td>€ 282</td>
<td>€ 2,387</td>
<td>€ 3,095</td>
<td>[18,21,22]</td>
</tr>
<tr>
<td><strong>Predominant source of healthcare funding:</strong></td>
<td>Obligatory insurance</td>
<td>Regular taxation</td>
<td>Obligatory insurance</td>
<td>[18,21,22]</td>
</tr>
</tbody>
</table>

Legend: *total population is set for the year 2013 in all countries; all other data are the latest possible;
Chapter 3

An overview of different reimbursement statuses and approaches in PE assessment of all EMA registered TCTs in Serbia, Scotland and the Netherlands is reported in a table given as an Appendix to this book (page 169). By the 15th of August 2014 there were 41 TCTs registered and these drugs referred to 70 TCTs’ indications with marketing authorisation by EMA.

In Serbia, out of the total number of TCTs’ indications issued by EMA, 20 of them (29%) are reimbursed (total of 11 TCT drugs). As much as 25 TCTs’ indications (36%) are still not registered by regulatory authorities in the country, and therefore, could not have had an application for reimbursement. For the same number of indications (25; 36%) there are no available information on the reimbursement status. Although registered, these drugs are either not yet submitted, currently under consideration or rejected in the past. None of reviewed indications and TCTs had publically available PE assessment reports.

Scottish SMC gave positive recommendation for 26 TCTs’ indications (37%), while it decided to reject as much as 30 (43%). Most of the negative decisions were related to the submitted applications of manufacturers (18; 26%), while SMC also gave short negative appraisals in the absence of manufacturers’ submissions (12; 17%). The manufacturers did not submit reimbursement applications for the rest of the TCTs indications (14; 20%), probably none of these were considered by the SMC. Regarding the PE assessment, it should be noted that 42 TCTs indications were followed with a full CUA (or cost minimisation analysis if appropriate) and BIA reports out of the total of 44 submissions. Focusing on the outcomes of PE assessments, ICERs differed from £1,790 to £376,475/QALY as estimated by the manufacturers. Among approved TCTs’ indications, ICERs varied from £1,790 to £56,343/QALY and only 5 of 26 positive recommendations were given to the TCTs with an ICER higher than £30,000/QALY. On the other hand, TCTs’ indications that gained negative recommendations corresponded with ICERs from £22,445 to £376,475/QALY and only 2 out of 18 of these cases the manufacturers’ estimates of ICER were below £30,000/QALY. Finally, decision modifiers were applied in the assessments of 7 TCTs’ indications and in 6 submissions they contributed to the positive decision.

Within the Dutch healthcare system TCTs indications were awarded with an initial positive reimbursement advice by CvZ/ZiNL in as much as 60 cases (86%). Notably, only 1 TCTs’ indication has been explicitly rejected by CvZ/ZiNL (1%), while remaining 9 (13%) are not reimbursed and it is not known if and when manufacturers submitted reimbursement dossiers for these TCTs’ indications. Among 60 initial approvals, 22 TCTs’ indications (31%) have been accepted conditionally and reassessment is needed with real-world data and full PE assessment. Yet, up to the cut off date of our study only 1 drug (trastuzumab) appeared with the reassessment report and the outcome of its reassessment was positive [26]. Out of 22 conditionally approved drugs, 15 have been accepted within earlier PREHO and 7 within new UFAP. All other accepted TCTs’ indications (38; 54%) do not require reassessment at this moment. Different are reasons for them to be exempted from the reassessment and, thus, from PE evaluation: 16 were previously accepted within regular extramural reimbursement system (reference pricing system) and, therefore, they do not require reassessment. Orphan drug designation was allowed for 10 of these TCTs’ indications, and an earlier PREHO did not require reassessment for orphan drugs. Budget impact below €2.5 million was the reason for 9 TCTs indication to be exempted from reassessment, as long as this annual limit is not crossed. Lastly, only 3 TCTs are still initially assessed, and requirement for reassessment is not known yet. As for PE assessments, although accepted TCTs’ indications (60) could have been exempted from
full PE assessment in compliance to the applied policies, 15 of them estimated cost per some unit of time, while 10 of them submitted full CUA with ICERS as outcome. Reported ICERS differed significantly, ranging from €6,412 to €164,262/QALY.

Discussion

We analysed differences in the reimbursement statuses of TCTs in the distinctive healthcare systems of Serbia, Scotland and the Netherlands. We examined the impact of the respective national approaches and special policies applied in PE assessment of TCTs on the final reimbursement decisions. Serbia, Scotland and the Netherlands are European healthcare systems with differentiating characteristics in population size and composition, epidemiology and economic parameters. Expectedly, we noted significant inequalities in the TCTs’ reimbursement statuses.

While in Serbia and Scotland reimbursement is granted to 20 and 26 TCTs’ indications respectively, in the Netherlands the number of mainly conditionally reimbursed TCTs’ indications is more than twofold higher and it reaches 60. We could not identify the reasons neither the values ascribed to the PE assessment in the Serbian reimbursement system due to lack of data. On the contrary, it is clear that differences observed between Scotland and the Netherlands could be at least partially explained by the different application of PE evaluation. Requirements of the Scottish SMC for full CUA for any therapy regardless its novelty or the seriousness of the disease they are treating led to this being an inevitable part of 95% of submissions for TCTs’ indications. It seems that the existence of clearly defined cost effectiveness threshold, with drugs considered cost ineffective if their ICER crosses £30,000/QALY, contributed to the negative SMC recommendation in 89% (16/18) of rejected manufacturer submissions. Among accepted submissions a huge majority (80%) had the ICER below that very same threshold. As for the Netherlands, the country with comparable economic background to Scotland, the previous PREHO and current UFAP allow adoption of expensive drugs without examining their PE value initially. Notably, only 1 submission (out of 61) of TCTs’ indications was explicitly rejected for reimbursement in the Netherlands.

Our comparison between Scotland and the Netherlands is in line with a recent paper on the subject of orphan drugs [27]. Major conclusions in that respect haven’t changed, rather have been strengthened with our current analysis. The current paper includes Serbia in the comparative approach, with the potential to draw on findings in Scotland and the Netherlands in continuing their development of the reimbursement process.

We feel that PE assessments should consistently be one of the determining factors in decisions on TCTs funding in all countries considered and beyond. It is however important to understand that designing regular CUAs presents a challenging task, in particular if patient groups are small or limited information from clinical trials is available. This is often the case with TCTs and extrapolations are required which bring uncertainties in CUAs. Also, PE assessments should not be decisive in itself, other factors should be weighted in an integrative approach. Currently, Scotland and the Netherlands seem to reflect two extremes of the options, with PE strictly applied in Scotland and therefore potentially decisive, and relatively loosely applied in the Netherlands. It should be noted that the postponing of PE assessment in the Netherlands is deliberately chosen with purpose of obtaining fast access for clinically effective new drugs and gaining sufficient real-world evidence with which PE will be conducted in future. Serbia could draw on this and develop an approach in between, taken the best of both countries. Obviously, with
relevantly different demographics, epidemiology and economics Serbia should adopt a policy designed to the specific local circumstances. In general, policies for reimbursements of new expensive drugs in terminal phases of diseases that come with the increments in survival, such as TCTs, are constantly changing and their outcomes are being reassessed. It remains debatable, whether these drugs’ PE values should be evaluated with the same approach as in general [28-30].

There are several limitations with which this review paper was confronted. Firstly and most importantly, in our choice of the countries for comparison we were limited with data accessibility. Although data on reimbursement decisions and PE assessment are broadly available in different countries, linguistic barriers prevented us choosing from all European countries. We limited our comparison to the countries of our origin, for which we could guarantee the highest level of data access. Secondly, the purpose of our comparison to illustrate diversities of existing European systems from the perspective of TCTs reimbursement was quite demanding. Without exact knowledge of all European health care systems, we cannot claim that we grasped all important differences. Still, we do believe that Serbia, Scotland and the Netherlands are typical examples of: (i) one South Eastern European health care system with PE assessment not fully implemented and health care expenditure per capita far below European average; (ii) one British health care system, renowned for the thorough PE assessment, with around the average expenditure in health care in Europe and (iii) one of the most frequently changing systems, with far above the European average health care expenditure and specific role of PE evaluation. Hopefully, this illustrated differences well enough.

Conclusions

Reimbursement statuses of TCTs considerably differ in three examined healthcare systems. Requirements and interpretation of cost effectiveness assessments and the level of its application affects the final reimbursement decisions. Within the systems under comparison, the Netherlands applies special approach for expensive and orphan drugs which postpones PE analyses, and this currently results in the highest proportion of reimbursed TCTs. In Scotland exemptions from standard PE analyses are not acceptable which leads to considerably lower numbers of reimbursed TCTs, comparable to that found in Serbia. Serbian healthcare authorities currently offer the least information on the process of drug’s reimbursement’ assessments and pharmacoeconomics is still to be fully implemented within this system. Serbia could draw on the experiences reported here for both other countries.

Conflict of interest statement

The authors indicate that they do not have any conflict of interest.

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PART II:

COST EFFECTIVENESS OF TARGETED CANCER THERAPIES