Purpose: To assess and compare the costs of first-line monoclonal antibodies (mAbs) treatment protocols in breast cancer, non-Hodgkin lymphoma and colorectal carcinoma in South-Eastern Europe.

Methods: A retrospective, bottom-up case series study design was implemented with one-year time horizon and payer’s perspective. The study sample size was 265 patients (breast cancer, N=137; colorectal cancer, N=44; and non-Hodgkin lymphoma, N=84), while treatment protocols included adjuvant mAbs: trastuzumab (N=137), bevacizumab (N=28), rituximab (N=16) and cetuximab (N=84). ICD-10 related resources use included history of medical services utilization, chronology (time out of service provision) and unit consumption of examinations, drugs prescribed, imaging, radiotherapy and surgical procedures provided etc., direct medical and lost productivity costs (€) across treatment groups during 2010-2013.

Results: The average length of observation was 125±97 days per patient. Total mean direct and indirect costs of care were: trastuzumab for breast cancer group €17,740 per patient; bevacizumab for colorectal carcinoma group €8,775 per patient; cetuximab for colorectal carcinoma group €27,181 per patient; and rituximab for non-Hodgkin lymphoma group €19,431 per patient. An average mAbs-treated patient incurred €17,897 costs of medical care. The total combined budget of these 330 patients was €4,742,775.

Conclusions: The use of mAbs strongly correlated with high costs in first-line cancer medical care and dominated other cost domains. Cetuximab-based treatment protocols in colorectal carcinoma patients was substantially more expensive compared to trastuzumab (C50), bevacizumab (C20), and rituximab (C80) alternatives. Extremely high costs of mAbs are the key-issue for Eastern European policy makers by crossing the upper limits of affordability in middle-income economies.

Key words: cancer, costs, monoclonal antibodies, Serbia, resource use

Introduction

Although the clinical efficacy of most mAbs is well documented in clinical trials [1], the heavy budget impact of these medicines can be felt in most European markets [2]. During the past few decades the overall pace of pharmaceutical expenditure growth in Europe was significantly faster compared to national gross domestic product (GDP) growth [3]. This is in line with similar market trends noticed in the United States [4] and Japan [5]. The arrival and marketing of novel targeted immunotherapy, although therapeutically promising in autoimmune disorders, for cancer it has put a challenging policy challenge on authorities in terms of reimbursement issues and...
affordability to the citizens in need [6].

The mAbs’ big step forward in extending survival [7] and improving the quality of life did not come without substantial additional cost. This can be seen in the example of colorectal carcinoma treatment with bevacizumab which extended survival rates while demanding a double to triple rise in drug acquisition expenses [8]. A particularly relevant issue is the consequences of dealing with adverse events of mAbs. The Uppsala Monitoring Centre (UMC) has noticed that their pharmacovigilance profile is quite different from that of most small-molecule pharmaceuticals [9]. Although hospital admissions due to mAbs-related toxicity represent a substantial burden, the clinical benefit seems to outweigh this risk [10].

Significant efforts to assess the impact of mAbs budget have been made worldwide [6]. Reliability of these assessments, nevertheless, is subject to bias due to sampling strategies and patient heterogeneity [11]. This is particularly the case in oncology due to the complexity of the clinical course and demanding resource use.

In this retrospective cost comparison analysis the authors focused on mAbs used in the treatment of breast cancer, non-Hodgkin lymphoma and colorectal carcinoma. These three malignancy groups were of particularly high relevance, being among the top four most expensive cancers to treat in the US in 2004, due to mAbs utilization [12].

The economic impact of these targeted immunotherapies remains to prove whether they provide satisfactory value-for-money in a real life setting [2]. According to the authors’ best knowledge there is a substantial knowledge gap on this issue in the Southeastern European region. An in-depth insight into costs of care in our case series study setting might provide useful grounds for further complete economic evaluations.

Methods

Ethics Committee Approval

The study was conducted in line with the Declaration of Helsinki and was approved by the regional Ethics Committee of the University Clinical Center Kragujevac, Serbia (Decision number 01-5978 issued on 28.05.2013).

Study design

A retrospective, bottom-up case series study design was implemented with one-year time horizon and payer’s perspective. The authors decided for a retrospective methodological approach on the grounds of processing tertiary care university clinic registry files for the central Serbia region, which provided insight into the clinical background of each case (e.g. tumor type, use of different diagnostic procedures and treatment data). Major cost drivers and determinants of resource consumption during oncological inpatient care were identified. Exact hospital admissions duration, frequency of physician consultations, laboratory and imaging examinations, pharmacotherapy, radiotherapy and surgical treatments and lost productivity data were acquired. The source of data on medical consumption were electronic hospital discharge invoices. Personal data remained protected during the study, in line with the legislation on biomedical research in human subjects in Serbia, via anonymous handling of patient files.

The authors had at their disposal the Financial Registry of the aforementioned University Clinic of Kragujevac. This retrospective study analysed resource use and costs of newly diagnosed cancer cases during a four-year period (2010-2013) and the sample represented inhabitants of this central Serbian region.

Setting

Serbia is an upper-middle income European economy which has made great progress of healthcare system transformation in line with models historically established in mature markets [13]. The central Serbian region of Sumadija, with a population of 297,000 inhabitants, is mostly an urban region located south of the capital Belgrade. It hosts several secondary care hospitals and one large University-associated tertiary care facility (1,297 beds). Cancer prevalence and incidence rates in this region are comparable to the national average [14]. The studied patients received first-line mAbs treatment following confirmation of diagnosis. Resource use and costs are attributed to this phase of disease.

Data

The tertiary care of in- and outpatient registry of discharge invoices contained extensive information on resource consumption of each single cancer-related episode of primary care visit and hospital in- or outpatient admission in the aforementioned period of time. Epidemiological and clinical background data were extracted from the hospitals patient records. Out of an existing pool of 6,182 admitted inpatients in a target facility within the observed time span, we have selected and retrospectively analysed 330 patients with a treatment based on mAbs protocols. These included patients with newly diagnosed, laboratory, imaging and histology-confirmed cancer on biopsy specimens; with any prescription of a mAb first-line treatment regimen; age above 18 years; and both sexes. Exclusion criteria where: age less than 18 years; absence of mAbs-based treatment protocol (cytotoxic drugs only); presence of another severe concomitant illness; and lack of significant study data.

Within the mAbs group each single patient had received first-line mAbs treatment with one of the fol-
lowing agents: rituximab for non-Hodgkin lymphoma, bevacizumab or cetuximab for colorectal carcinoma and trastuzumab for HER2-positive breast cancer cases, depending on the exact indication field contained in the official marketing licence. The mAbs administration was adjuvant and patients received conventional cytotoxic treatment according to internationally accepted oncological protocols and evidence-based guidelines [15-17]. Indirect productivity loss attributed to patient care, absenteeism, working days loss and premature working disability were calculated based on the Grossman's human capital approach [18].

Data analysis

Data on complete tertiary care level in- and outpatient medical services consumed allowed for micro costing. Based on precise hospital discharge invoices and patient files, access was provided to detailed data on patient diagnostics and treatment services utilization related to main oncology morbidity and its consequences. An in-depth costs analysis of mAbs-treated patients was carried out. Additional assessment and comparison of group differences among alternative treatment protocols for the respective malignant disorders were analysed (trastuzumab treated HER-positve breast cancer; rituximab treated non-Hodgkin lymphoma (large B-cell and follicular lymphoma cases); bevacizumab and cetuximab-treated colorectal carcinoma). Costs related to health service utilization such as physician consultations, diagnostics (such as imaging, lab tests), surgical interventions, radiation therapy regimens and prescription of pharmaceuticals across classes, were also registered and analysed.

Theory/calculation

The underlying assumption under the research question stated in this study was that major mAbs-based cancer treatment protocols incur substantially different hospital costs of care. The aim was to clarify and reveal these differences for the first time in a pioneering attempt in a broad Southeastern European region.

Practically speaking, electronic database patient files were used to extract and analyse in-depth data with regards to resource use patterns and costs.

Statistics

Complete statistical analyses were carried out using the PASW Statistics 18.0 software and Microsoft Office Excel 2007. Categorical variables were presented as frequency of certain variables, while statistical significance of differences was tested with the chi-square test. Continuous variables were summarized as mean (M) and standard deviation (SD) with range values (minimum-maximum) and 95% confidence interval (95%CI). Normality of the data was assessed using the Kolmogorov-Smirnov test. ANOVA was used in normally distributed data while analysis of financial resources spent was done by using non-parametric tests such as Kruskal-Wallis test (due to large standard deviations). All analyses were estimated at p<0.05 level of statistical significance.

Results

The sample size consisted of 265 patients (70 male and 195 female, mean age 58.18±12.18 years, Min 19- Max 84 years). The patients were divided in four treatment protocol, related to ICD-10 diagnostic groups and core mAb agents administered. The average length of observation was 125.75±97.22 (95% CI; 116-139) days per patient, and this period refers to the initial period of treatment following diagnosis. A total of 44 colorectal carcinoma patients were conventionally treated by FOLFOX protocol (infusional 5-fluorouracil/leucovorin and oxaliplatin). Out of them, 28 patients were treated with additional bevacizumab while 16 patients were treated with FOLFOX+cetuximab [19,20]. The group of 137 HER2-positive breast carcinoma patients received adjuvant treatment with trastuzumab [21] after having received conventional cytotoxics such as 5-fluorouracil+adriamycin+ cyclophosphamide or 5-fluorouracil+epirubicin+cyclophosphamide or adriamycin+cyclophosphamide+paclitaxel/docetaxel. There were 84 non-Hodgkin lymphoma patients receiving rituximab-based treatment [22,23] along with fludarabin+cyclophosphamide+prennisolone (FCP) or fludarabin+mitoxanthrone+prednisolone (FMP) or fludarabin+cyclophosphamide [24] (Table 1).

Analysis showed that an average mAbs-treated patient incurred €17,897 (95% CI €16,399-€19,396). Its costs matrix structure consisted of €15,625 (95% CI €14,242 - €17,009) mean costs of inpatient medical care per patient, € 242 (95% CI €167 - €318) of total outpatient costs and € 2,029 (95% CI € 1,847 - €2,212) of indirect cost at the first-line treatment of cancer. Major contributors to the costs of care were: oncology nursing care €216,052 (5%); physician consultations € 5,221 (≤0.5%); laboratory analyses € 68,514 (2%); imaging diagnostics €31,75 (1%); interventional radiology € 4,998 (≤0.5%); pharmaceuticals (without mAbs) €253,224 (6%); surgery €10,786 (≤0.5%); radiation therapy €62,404 (2%); and €3,552,076 (84%) of mAbs acquisition costs (Tables 2 and 3).

Trastuzumab-treated breast cancer cases imposed mean costs of €15,819 (95% CI €12,394-€15,244) per patient. Bevacizumab-treated colorectal carcinoma inflicted mean costs of €5,890 (95% CI €4,850-€6,949), while cetuximab-treated ones
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were €23,008 (95% CI €10,746- €35,271) per patient. Rituximab-treated non-Hodgkin lymphoma cases imposed mean costs of €13,402 (95% CI €11,597- €15,207) per patient. An average mAbs-treated patient incurred mean costs of €13,658 (95% CI €12,569- €14,746) of medical care. Assessment of lost productivity costs was based on available data on employment status, absenteeism, opportunity cost of family member taking home care and official average gross annual salaries in Serbia. Mean per patient values of indirect costs were lowest in colorectal carcinoma bevacizumab group, while highest in colorectal carcinoma cetuximab-based protocol (Figures 1 and 2).

The total combined budget impact of these 265 patients was €4,742,775.

Discussion

The aim of this study was to compare mAbs-related resource use and costs in three important malignancies. These particular disorders (breast cancer, colorectal carcinoma and non-Hodgkin lymphoma) were selected because they are officially recognized indications for mAbs-based protocols by the Republican Health Insurance Fund in Serbia. According to the current legislation, mAbs-based cancer treatment protocols are fully reimbursed only for these ICD-10 diagnostic groups. Keeping in mind the upper-middle income economy setting and the low affordability of these expensive medicines among ordinary citizens, the vast majority of mAbs-treated patients

Table 1. Patients demographics and mAbs use

<table>
<thead>
<tr>
<th>Sample size</th>
<th>Breast cancer trastuzumab treated</th>
<th>Colorectal carcinoma bevacizumab treated</th>
<th>Colorectal carcinoma cetuximab treated</th>
<th>Non-Hodgkin lymphoma rituximab treated</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis, years (M±SD)</td>
<td>137</td>
<td>28</td>
<td>16</td>
<td>84</td>
<td>N/A</td>
</tr>
<tr>
<td>Length of observation (days) (M±SD)</td>
<td>55.01 ± 10.49</td>
<td>60.56 ± 8.92</td>
<td>68.19 ± 7.35</td>
<td>60.73 ± 14.54</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Outpatient physician consultations (M±SD)</td>
<td>158.20 ± 103.56</td>
<td>61.54 ± 1.07</td>
<td>80.38 ± 59.17</td>
<td>109.19 ± 84.95</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Inpatient physician consultations (M±SD)</td>
<td>5.76 ± 4.95</td>
<td>5.11 ± 5.33</td>
<td>6.69 ± 4.76</td>
<td>0.05 ± 1.41</td>
<td>0.004</td>
</tr>
<tr>
<td>Frequency of hospital admissions (M±SD)</td>
<td>7.18 ± 4.11</td>
<td>4.86 ± 2.41</td>
<td>3.58 ± 2.16</td>
<td>4.23 ± 2.61</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total duration of all hospital admissions (days) (M±SD)</td>
<td>11.40 ± 9.75</td>
<td>12.64 ± 7.28</td>
<td>74.44 ± 145.58</td>
<td>37.12 ± 29.17</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MABs unit consumption (M±SD)</td>
<td>8.56 ± 5.22</td>
<td>7.29 ± 5.59</td>
<td>126.94 ± 137.71</td>
<td>25.26 ± 17.50</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

M: mean, SD: standard deviation, mAbs: monoclonal antibodies, N/A: not applicable
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in the country will suffer from one of these three particular malignancies.

There was no statistically significant difference in our retrospective case series analysis between total costs of care (direct hospital in- and outpatient+indirect costs) between these four treatment protocols (p values ≤ 0.01). As previously reported in results section, these differences where vast and present across variety of cost domains (Table 2; Table 3). Cetuximab-treated colorectal carcinoma patients were substantially more expensive compared to others while bevacizumab treated cases had the weakest budget impact among all. These differences could be attributed to the differences in patterns of medical services utilization like mAbs dosing regimens between treatment protocols, and frequency and duration of hospital admissions (Table 1). Substantial cost differences among these three particular ICD-10 malignancy groups have already been observed while immunotherapy of non-Hodgkin lymphoma was associated with $285 million, metastatic colorectal carcinoma with $73 million, and metastatic breast cancer amounted to $12 million cost increase in the US in 2004 [12].

Through the years of post marketing experience in clinical oncology practice worldwide, some mAbs exhibited satisfactory therapeutic effectiveness [25]. This was particularly the case in combination with primarily applied pharmacogenomics diagnostics detecting responsive genotypes [26]. Clinical applications of bevacizumab in colorectal cancer, trastuzumab in breast cancer and rituximab in large B-cell [27] and follicular lymphoma cases, together with other mAbs’ indications which gained marketing approval in different countries, seem to prolong survival and improve the quality of life of some of these patients [28]. Fratino et al. [29] reported that in elderly cancer patients lower utilization of mAbs was noticed, which raises the issue of access equity to these expensive medicines [30]. Usefulness of these protocols and their promising future imply serious issues with regards to affordability of such care, even in high-income economies [31]. The true value in health attributable to these adjuvant treatment protocols soon became an issue of international debate [32,33]. Due to different national policy practices towards mAbs reimbursement, regardless of the EMEA’s recommendations, ac-

<table>
<thead>
<tr>
<th>Table 2. Cost matrix of initial oncological care (expressed in Euros (€); mean per patient values)</th>
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<tbody>
<tr>
<td><strong>M/SD/Min/Max/95% CI</strong></td>
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<tr>
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<tr>
<td><strong>Breast cancer – trastuzumab treated</strong></td>
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<tr>
<td><strong>Colorectal carcinoma – bevacizumab treated</strong></td>
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<td><strong>Colorectal carcinoma – cetuximab treated</strong></td>
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<tr>
<td><strong>Non-Hodgkin lymphoma – rituximab treated</strong></td>
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<td><strong>p value</strong></td>
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</table>

For abbreviations see footnote of Table 1
Table 3. Major cost domains of initial monoclonal antibody-based cancer treatment (expressed in Euros(€); mean per patient values)

<table>
<thead>
<tr>
<th>M/SD/Min/Max/ 95% CI</th>
<th>Breast cancer trastuzumab treated</th>
<th>Colorectal carcinoma bevacizumab treated</th>
<th>Colorectal carcinoma cetuximab treated</th>
<th>Non-Hodgkin lymphoma rituximab treated</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oncology medical care</td>
<td>320 (318, 1,336, 1,689)</td>
<td>1,356 (2,585, 1,652)</td>
<td>56 (10,661, 11,732)</td>
<td>1,340-2,058</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Laboratory analysis</td>
<td>18 (37, 751)</td>
<td>227 (380, 579)</td>
<td>0 (15)</td>
<td>2,812</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Imaging diagnostics</td>
<td>10 (7, 322)</td>
<td>196 (443, 443)</td>
<td>0 (0)</td>
<td>1,652</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Interventional radiology</td>
<td>3 (19, 45)</td>
<td>19 (6)</td>
<td>0 (1)</td>
<td>283</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pharmaceuticals (without mAbs)</td>
<td>594 (1,356, 1,390)</td>
<td>927 (1,371, 1,390)</td>
<td>975 (2,210)</td>
<td>917-1,862</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Surgery</td>
<td>6 (14, 107)</td>
<td>35 (84)</td>
<td>1 (2)</td>
<td>491</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Radiation therapy</td>
<td>459 (38, 77)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Monoclonal antibodies</td>
<td>13,819 (5,890, 23,008)</td>
<td>13,402 (25,025, 8,440)</td>
<td>449 (1,243, 8,440)</td>
<td>11,597-15,207</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

For abbreviations see footnote of Table 1
cess to targeted immunotherapy in oncology remains uneven across European Union [34]. Unlike in Western countries [35], cost-effectiveness estimates on mAbs administration in oncology have been rather seldom in published literature in the Eastern European region [36,37]. These assessments provide a necessary base for reimbursement decisions in various national health systems such as Canada [38]. The reported mAbs acquisition costs of cancer treatment in Serbia of €13,658 per patient (= $19,810) is approximately half of the lower limit of the range of $45,000-191,000 in 2009 (total out-of-pocket drug acquisition expense), recently reported in the US [39]. Average per capita gross domestic product and the healthcare expenditure gap between these two economies is overreaching such a ratio by far. We can assume an unsustainable budget impact of mAbs, which are currently mostly reimbursed out of public health insurance funds in Eastern Europe [40]. Out-of-pocket acquisition of such expensive pharmaceuticals is virtually unaffordable to the majority of ordinary citizens [41]. Eastern European middle-income environment is known for its lower wages compared to high-income neighboring countries. But it is essential to emphasize that drug acquisition costs follow global market pricing and remain only slightly lower than in Western Europe [13]. In most published evidence in high-income markets, mAbs budget impact remains crucial compared to all other costs of care [6]. A cost-saving strategy on mAbs was dose rounding proposed by Winger et al. [42]. Recent findings from the Balkan region indicate that imaging diagnostics and radiation therapy remain some of the essential contributors to the overall costs of cancer medical care [43,44]. Current patterns of Oncology healthcare funding throughout Eastern Europe will ultimately lead to legislative framework development on biologicals in the region [45]. Grounded in the aforementioned remarks, we believe that findings from the upper-middle income countries should be applicable to the challenging resource allocation strategies of other Eastern European middle-income countries.

Study limitations

A tertiary care University hospital’s registry on in- and outpatient medical services provided grounds for this research. Classical retrospective database analysis was applied, while a rather limited number of 265 (4.3%) patients received expensive mAbs treatment out of 6,182 patients admitted to the regional Oncology and Radiotherapy Centre. Besides a narrow indication field, this was the second most important reason for modest sample size [46]. Observation of similar stage and grade carcinomas within the same ICD-10 diagnostic code would have been an alternative to establish a control group on a matched-case basis [47]. This approach was not followed, due to the fact that in a broader previous pilot study cancer patients conventionally treated without mAbs, incurred approximately seven-fold lower costs and thus were not regarded comparable in terms of budget impact [48]. The selection of only 265 patient files from those admitted due to newly diagnosed cancer in the period observed, may limit sample representativeness. It should be noted, however, that these cases constitute the vast majority of those treated with mAbs-based protocols and were selected in order to maximize the sample size. A more lengthy time horizon and an in-depth follow up of clinical outcomes would be helpful for more precise estimates on survival and terminal care. Unfortunately such an additional effort was out of the scope and budget of this trial.

Conclusions

Regardless of the limited sample size, this cost of illness could be helpful to decision-makers due to the very limited amount of published evidence on health economic consequences of mAbs administration throughout Eastern Europe. Our study shows that even among most expensive adjuvant mAbs protocols in cancer, there are substantial differences in cost patterns. Getting familiar with such cost comparisons would allow for more careful budgeting and resource allocation in oncology clinics following demand for services.

Some of the key strategies proposed for cost containment of these sky rocketing costs of oncological care [49] were to introduce more affordable generic versions of these medicines [3]. Owing to the unique technology of mAbs [50] this step will not likely happen for another few additional years until the first marketing approvals will be granted [51]. Another commonly applied policy to provide cutting-edge medical technology to those in need, while limiting its budget impact, is narrowing the indication field to those patients likely to benefit most from the treatment and to avoid serious side effects [52]. Manufacturing process costs, like in other major pharmaceutical industry research and development (R&D) mainstreams, are about to decrease substantially with time [53]. Substantial presence of mAbs among top-profit, blockbuster
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Drugs should keep us aware of the vital interest in these agents for the pharmaceutical industry worldwide [54,55]. Oncologists should also remain aware of an essential contribution of this expensive targeted immunotherapy to prolong survival in many kinds of cancer [56]. Industrial commitment to R&D investment in this area will likely bring future benefits for many patients currently regarded incurable [57]. Findings on cost differences among major mAbs-based cancer treatment protocols brought with this study, should be regarded particularly essential for Western Balkans region and its largest market of Serbia, were the value of turnover has increased almost 2000% during the past decade [58]. Therefore, more cost-effective national reimbursement policy could provide essential savings to Balkan health systems.

Acknowledgements

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