JBUON 2014; 19(3): 1111-1120
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

SPECIAL ARTICLE

Costs differences among monoclonal antibodies-based first-line oncology cancer protocols for breast cancer, colorectal carcinoma and non-Hodgkin's lymphoma

Mihajlo Jakovljevic[1], Florian Gutzwiller[2], Matthias Schwenkglenks[2], Olivera Milovanovic[3], Nemanja Rancic[4], Mirjana Varjacic[5], Dobrivoje Stojadinovic[6], Aleksandar Dagovic[7], Klazien Matter-Walstra[2]

[1]Department of Pharmacology and Toxicology, Faculty of Medical Sciences, University of Kragujevac, Kragujevac, Serbia; [2]Institut für Pharmazeutische Medizin (ECPM), Basel, Switzerland; [3]Department of Pharmacy, Faculty of Medical Sciences, University of Kragujevac, Kragujevac, Serbia; [4]Centre for Clinical Pharmacology, Medical Faculty, Military Medical Academy, University of Defense, Belgrade, Serbia; [5]Gynaecology Clinic, University Clinical Center Kragujevac, Kragujevac, Serbia; [6]Urology Clinic, University Clinical Center Kragujevac, Kragujevac, Serbia; [7]Oncology and Radiation Therapy Center, Clinical Center Kragujevac, Kragujevac Serbia;

Summary

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

Correspondence to: Mihajlo Jakovljevic, MD, PhD. Department of Pharmacology and Toxicology, Faculty of Medical Sciences, University of Kragujevac, Svetozara Markovica 69, 34000 Kragujevac, Serbia. Tel/Fax: +38134306800,
E-mail: jakovljevicm@medf.kg.ac.rs
Received: 07/04/2014; Accepted: 25/04/2014

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 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-positive 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+prednisolone (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 €13,819 (95% CI €12,394-€15,244) per patient. Bevacizumab-treated colorectal carcinoma inflicted mean costs of €5,890 (95% CI €4,830- €6,949), while cetuximab-treated ones

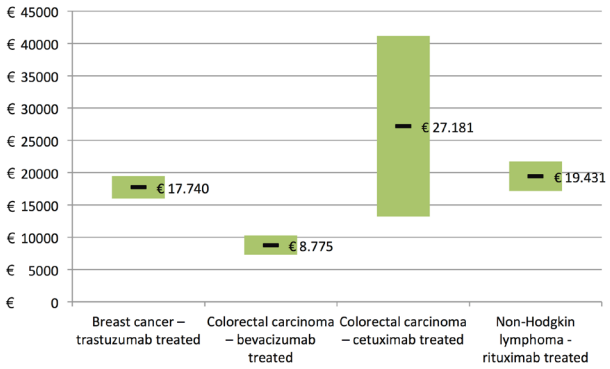

Figure 1. Total (direct in- and out-patient+indirect) costs differences among mAbs-treated cancer patients (mean per patient values ± CI 95%).

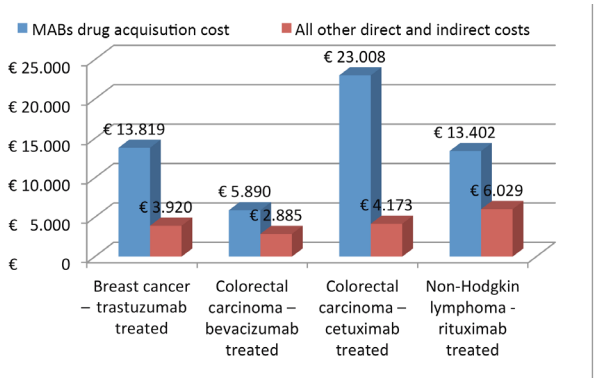

Figure 2. mAbs drug acquisition costs vs all other direct medical (in- and out-patient) and indirect costs (oncology-nursing medical care; physician consultations; laboratory analysis; imaging diagnostics; interventional radiology; pharmaceuticals (without mAbs); surgery and radiation therapy) of initial cancer treatment (mean values in € per patient).

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

	Breast cancer trastuzumab treated	*Colorectal carcinoma bevacizumab treated*	*Colorectal carcinoma cetuximab treated*	*Non-Hodgkin lymphoma rituximab treated*	*p value*
Sample size	137	28	16	84	N/A
Age at diagnosis, years (M±SD)	55.01 ± 10.49	60.36 ± 8.92	68.19 ± 7.35	60.73 ± 14.54	<0.001
Length of observation (days) (M±SD)	158.20 ± 103.56	61.54 ± 1.07	80.38 ± 59.17	109.19 ± 84.95	<0.001
Outpatient physician consultations (M±SD)	5.76 ± 4.95	5.11 ± 5.33	6.69 ± 4.76	0.05 ± 1.41	0.004
Inpatient physician consultations (M±SD)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	1.49 ± 3.63	<0.001
Frequency of hospital admissions (M±SD)	7.18 ± 4.11	4.86 ± 2.41	3.38 ± 2.16	4.23 ± 2.61	<0.001
Total duration of all hospital admissions (days) (M±SD)	11.40 ± 9.75	12.64 ± 7.28	74.44 ± 145.58	37.12 ± 29.17	<0.001
MABs unit consumption (M±SD)	8.56 ± 5.22	7.29 ± 5.59	126.94 ± 137.71	25.26 ± 17.50	<0.001

M: mean, SD: standard deviation, mAbs: monoclonal antibodies, N/A: not applicable

Table 2. Cost matrix of initial oncological care (expressed in Euros (€); mean per patient values)

M/SD/Min/Max/95% CI	*Outpatient medical costs*	*Inpatient medical costs*	*Indirect costs*	*Total costs*
Breast cancer – trastuzumab treated	445	14,788	2,507	17,740
	816	8,951	1,620	10,411
	0	1,558	15	1,654
	779	47,507	5,821	52,547
	309-581	13,294-16,281	2,237-2,777	16,003-19,477
Colorectal carcinoma – bevacizumab treated	59	7,721	995	8,775
	210	4,062	760	4,666
	0	1,292	34	1,341
	1,126	17,030	3,485	19,381
	-19-137	6,217-9,225	714-1,277	7,047-10,504
Colorectal carcinoma – cetuximab treated	104	25,748	1,329	27,181
	184	27,946	1,019	28,530
	0	1,362	17	1,396
	535	90,883	3,787	91,885
	14-194	12,055-39,441	830-1,828	13,202-41,161
Non-Hodgkin lymphoma - rituximab treated	0	17,699	1,733	19,431
	1	9,792	1,309	10,657
	0	2,444	15	2,564
	11	44,426	4,794	48,554
	0-1	15,605-19,792	1,453-2,013	17,152-21,710
p value	<0.001	<0.001	<0.001	<0.001

For abbreviations see footnote of Table 1

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

M/SD/Min/Max/ 95% CI	*Breast cancer trastuzumab treated*	*Colorectal carcinoma bevacizumab treated*	*Colorectal carcinoma cetuximab treated*	*Non-Hodgkin lymphoma rituximab treated*	*p value*
Oncology medical care	320	318	1, 336	1,689	<0.001
	665	198	2, 585	1,632	
	13	29	37	56	
	508	743	10,661	11,732	
	209-431	245-392	70-2,603	1,340-2,038	
Laboratory analysis	18	37	227	731	<0.001
	30	40	380	579	
	0	0	0	15	
	178	155	1,162	2,812	
	13-23	22-52	41-413	607-855	
Imaging diagnostics	10	7	196	322	<0.001
	31	16	446	443	
	0	0	0	0	
	315	70	1,755	1,652	
	5-15	1-13	-23-414	227-417	
Interventional radiology	3	19	19	45	<0.001
	3	20	23	56	
	0	1	0	1	
	12	106	77	283	
	3-3	11-26	7-30	33-57	
Pharmaceuticals (without mAbs)	594	1,436	927	1,390	<0.001
	1,203	1,371	975	2,210	
	0	69	6	5	
	6,006	4,967	2,903	12,989	
	394-795	929-1,944	449-1,404	917-1,862	
Surgery	6	14	35	107	<0.001
	5	14	37	84	
	0	1	1	2	
	27	70	120	491	
	5-7	9-19	17-53	89-125	
Radiation therapy	439	38	77	0	<0.001
	809	198	166	0	
	0	0.00	0	0	
	2,748	1,050	462	0	
	304-574	-36-111	-5-158	0-0	
Monoclonal antibodies	13,819	5,890	23,008	13,402	<0.001
	8,539	2,859	25,025	8,440	
	1,544	1,109	1,243	449	
	47,029	11,642	78,652	33,804	
	12,394-15,244	4,830-6,949	10,746-35,271	11,597-15,207	

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

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

The Serbian Academy of Sciences and Arts – University of Kragujevac branch and the Ministry of Science and Education of the Republic of Serbia have jointly co-financed this study through Grant N°175014.

References

1. von Mehren M, Adams GP, Weiner LM. Monoclonal antibody therapy for cancer. Annu Rev Med 2003;54:343-369.
2. Simoens S. Health economics of market access for biopharmaceuticals and biosimilars. J Med Econ 2009;12:211-218.
3. Ess SM, Schneeweiss S, Szucs TD. European healthcare policies for controlling drug expenditure. Pharmacoeconomics 2003;21:89-103.
4. Center for Medicare & Medicaid Services. Updated and extended national health expenditure projections, 2010-2019. Washington, DC: US Department of Health & Human Services, 2011.
5. Ogura S. Revisiting the Japanese comprehensive reimbursement scheme for the elderly outpatients during 1996-2002 period: How it affected Japanese healthcare practices. Japan J Health Economics Policy 2010;21:191-212.
6. Wild F. Increases in pharmaceutical expenditures of PHI by monoclonal antibodies. Versicherungsmedizin 2013;65:91-93.
7. Dalle S, Thieblemont C, Thomas L, Dumontet C. Monoclonal antibodies in clinical oncology. Anticancer Agents Med Chem 2008;8:523-532.
8. Schrag D. The price tag on progress--chemotherapy for colorectal cancer. N Engl J Med 2004;351:317-319.
9. Sekhon BS, Saluja V. Biosimilars: an overview. Biosimilars 2011;1:1-11.
10. Akiyama S. Specific adverse events caused by monoclonal antibodies, focusing on the prophylaxis and management. Nihon Rinsho 2012;70:2199-2204.
11. Puder KL, Wood LL, Sherrill A. Health economics with retrospective data: selection bias issues. J Int Med Res 1997;25:45-51.
12. Shih YC, Elting LS, Pavluck AL, Stewart A, Halpern MT. Immunotherapy in the Initial Treatment of Newly Diagnosed Cancer Patients: Utilization Trend and Cost Projections for Non-Hodgkin,s Lymphoma, Metastatic Breast Cancer, and Metastatic Colorectal Cancer. Cancer Investig 2010;28:46-53.
13. Jakovljevic M, Jovanovic M, Lazic Z et al. Current efforts and proposals to reduce healthcare costs in Serbia. Serb J Exp Clin Res 2011;12:161-163.
14. Milijus D, Zivkovic S, Bozic Z (Eds): Cancer incidence and mortality in central Serbia. Report No. XII. Beograd: Institute of Public Health of Serbia "Dr Milan Jovanovic Batut", 2012.
15. El Saghir NS, Eniu A, Carlson RW et al. Locally advanced breast cancer: treatment guideline implementation with particular attention to low- and middle-income countries. Cancer 2008;113(8 Suppl):2315-2324.
16. Vogl TJ, Schmiegel W, Pox C et al. S3 guideline--Diagnosis and treatment of colorectal carcinoma: relevance for radiologic imaging and interventions. Rofo 2013;185:699-708.
17. Faber LM, van Agthoven M, Uyl-de Groot CA, Löwenberg B, Huijgens PC. Diagnosis and treatment of non-Hodgkin lymphoma in Netherlands: variation in guidelines and in practice. Ned Tijdschr Geneeskd 2000;144:1223-1227.
18. Zweifel P. The Grossman model after 40 years. Eur J Health Econ 2012;13:677-682.
19. Zhao Z, Pelletier E, Barber B et al. Patterns of treatment with chemotherapy and monoclonal antibodies for metastatic colorectal cancer in Western Europe. Curr Med Res Opin 2012;28:221-229.
20. Hsu JY, Wakelee HA. Monoclonal antibodies targeting vascular endothelial growth factor: current status and future challenges in cancer therapy. BioDrugs 2009;23:289-304.
21. Fornier M, Esteva FJ, Seidman AD. Trastuzumab in combination with chemotherapy for the treatment of metastatic breast cancer. Semin Oncol 2000;27(6 Suppl 11):38-45; discussion 92-100.

22. Tilly H, Vitolo U, Walewski J et al. Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012 (Suppl 7):vii78-82.
23. López-Guillermo A, Caballero D, Canales M et al. Clinical practice guidelines for first-line/after-relapse treatment of patients with follicular lymphoma. Leuk Lymphoma 2011;52 (Suppl 3):1-14.
24. Gershanovich ML, Tikhonova VV. Use of fludarabin in conjunction with other cytostatics in the treatment of non-Hodgkin lymphoma resistant to standard chemotherapy. Vopr Onkol 2004;50:602-604.
25. Aapro MS. Biosimilars in oncology: current and future perspectives, Generics and Biosimilars Initiative Journal (GaBI Journal) 2012;2(2): Epub ahead of print. DOI: 10.5639/gabij.2013.0202.023
26. Blank PR, Moch H, Szucs TD, Schwenkglenks M. KRAS and BRAF mutation analysis in metastatic colorectal cancer: a cost-effectiveness analysis from a Swiss perspective. Clin Cancer Res 2011;17:6338-6346.
27. Johnsen HE, Haioun C, Lugtenburg PJ et al. Importance of granulocyte colony-stimulating factor prophylaxis in therapy with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone given every 14 days for diffuse large B-cell lymphoma in routine clinical practice. Leuk Lymphoma 2012;53:982-984.
28. Gerber DE. Targeted therapies: a new generation of cancer treatments. Am Fam Physician 2008;77:311-319.
29. Fratino L, Crivellari D, Spina M et al. Use of biological drugs in elderly cancer patients: A sustainable reality? A mono-institutional experience. Int J Clin Oncol 2007;25,18 (Suppl):19665 (meet abstr).
30. Murata C, Yamada T, Chen CC, Ojima T, Hirai H, Kondo K. Barriers to health care among the elderly in Japan. Int J Environ Res Public Health 2010;7:1330-1341.
31. Cohen J, Wilson A. New challenges to medicare beneficiary access to mAbs. MAbs 2009;1:56-66.
32. Epstein RJ, Cheung BM. Loading doses for costly cancer biologicals: sound pharmacology or unnecessary extravagance? Eur J Cancer 2008;44:1488-1492.
33. Tigue CC, Fitzner KA, Alkhatib M, Schmid E, Bennett CL. The value of innovation: the economics of targeted drugs for cancer. Target Oncol 2007;2:113-119.
34. Tirelli U, Berretta M, Bearz A, Carbone A. Grouping of molecularly targeted anti-cancer agents based on cost-effectiveness analysis. Eur Rev Med Pharmacol Sci 2011;15:1355-1356.
35. Neyt MJ, Albrecht JA, Clarysse B, Cocquyt VF. Cost-effectiveness of Herceptin: a standard cost model for breast-cancer treatment in a Belgian university hospital. Int J Technol Assess Health Care 2005;21:132-137.
36. Brodszky V, Orlewska E, Pentek M, Karpati K, Skoupa J, Gulacsi L. Challenges in economic evaluation of new drugs: experience with rituximab in Hungary. Med Sci Monit 2010;16:SR1-5.
37. Kos M, Obradovic M, Mrhar A. Accessibility to targeted oncology drugs in Slovenia and selected European countries. Eur J Cancer 2008;44:408-418.
38. Chabot I, Rocchi A. How do cost-effectiveness analyses inform reimbursement decisions for oncology medicines in Canada? The example of sunitinib for first-line treatment of metastatic renal cell carcinoma. Value Health 2010;13:837-845.
39. Leonard CE, Freeman CP, MacCurdy T et al. Utilization and cost of anticancer biologic products among Medicare beneficiaries, 2006–2009: Data Points #6. In: Data Points Publication Series [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2011. http://www.ncbi.nlm.nih.gov/books/NBK65148/
40. Jakovljevic MB. Resource allocation strategies in Southeastern European health policy. Eur J Health Econ 2013;14:153-159.
41. Ilić MS. Pharmacoeconomic analysis of antineoplastics at the Oncology Institute of Vojvodina from 2005 to 2008. Archive Oncol 2009;17:78-79.
42. Winger BJ, Clements EA, DeYoung JL et al. Cost savings from dose rounding of biologic anticancer agents in adults. J Oncol Pharm Pract 2011;17:246-251.
43. Jakovljevic M, Rankovic A, Racic N et al. Radiology Services Costs and Utilization Patterns estimates in Southeastern Europe - A Retrospective Analysis from Serbia. Value Health Regional Issues 2013;2:218-225.
44. Ranković A, Rancić N, Jovanovic M et al. Impact of imaging diagnostics on the budget--are we spending too much? Vojnosanit Pregl 2013;70:709-711.
45. Gulácsi L. Future challenges for health economics and health technology assessment of biological drugs. Eur J Health Econ 2010;11:235-238.
46. Motheral B, Brooks J, Clark MA et al. A checklist for retrospective database studies--report of the ISPOR Task Force on Retrospective Databases. Value Health 2003;6:90-97.
47. Haley ML, Gerszten PC, Heron DE, Chang YF, Atteberry DS, Burton SA. Efficacy and cost-effectiveness analysis of external beam and stereotactic body radiation therapy in the treatment of spine metastases: a matched-pair analysis. J Neurosurg Spine 2011;14:537-542.
48. Radovanović A, Dagović A, Jakovljević M. Economics of cancer related medical care: Worldwide estimates and available domestic evidence. Archive Oncol 2011;19:59-63.
49. Malik NN. Controlling the cost of innovative cancer therapeutics. Nat Rev Clin Oncol 2009;6:550-552.
50. Knezevic I, Griffiths E. Biosimilars--global issues, national solutions. Biologicals 2011;39:252-255.
51. Konski AF. Generic Biologics - A Comparative Analysis of Regulatory Review. BioProcess Intern 2011;9:34-39.
52. Roger SD, Goldsmith D. Biosimilars: it's not as simple as cost alone. J Clin Pharm Ther 2008;33:459-464.
53. Farid SS. Process economics of industrial monoclonal antibody manufacture. J Chromatogr B Analyt Technol Biomed Life Sci 2007;848:8-18.
54. Scolnik PA. MAbs: a business perspective. MAbs 2009;1:179-184.
55. Ziegelbauer K, Light DR. Monoclonal antibody therapeutics: Leading companies to maximise sales and market share. J Commercial Biotechnol 2007;14:65-72.

56. Uyl-de Groot CA, de Groot S, Steenhoek A. The economics of improved cancer survival rates: better outcomes, higher costs. Expert Rev Pharmacoecon Outcomes Res 2010;10:283-292.
57. Yamada T, Chia-Ching C, Tadashi Y, I-Ming C, John D. Worrall Pharmaceutical Price Control Policy, Pharmaceutical Innovation, and Health Durability. Open Pharmacoecon Health Econ J 2010;2:34-46.
58. Jakovljevic MB. Oncology monoclonal antibodies expenditure trends and reimbursement projections in the emerging Balkan market. Farmeconomia. Health economics and therapeutic pathways 2014;15:27-32.