Monoclonal antibodies at the Oncology Institute of Vojvodina – 5-year expenditure

Marija Jelić[1], Darjana Jovanović[1,2], Lazar Popović[1,2], Dubravka Striber-Devaja[1]

SUMMARY

Background: *In the second half of the twentieth century, cancer treatment options evolved with more sophisticated selection of targets for cancer therapy, which led to the development of more intelligent drugs directed against these specific targets. One group of pharmaceutical molecules with specific and unique properties against (or for) a well-defined molecular target is monoclonal antibodies (mAbs). The purpose of this study was to show the expenditure of mAbs at the Oncology Institute of Vojvodina from 2007 to 2011. Next, to display the number of patients treated with mAbs and therapy cycles, for each indication.*

Methods: *We used software programs Lirpis and LWM for collecting the data regarding mAbs expenditure from April 2007 to 2011. The comments about the situation in Serbia were given with the review on the FDA approvals.*

Results: *The results showed the increase in number of ampoules dispensed from the pharmacy from 2007 to 2010, and a slight decrease in 2011 for all mAbs. With 4070 vials of rituximab, 195 patients were treated. The average number of therapy cycles was 7.34. With total number of 4341 of trastuzumab, we treated 310 patients, with average number of cycles 12.27. With 1343 ampoules of bevacizumab, we treated 92 patients. The average number of cycles was 6.63. With 7051 ampoules of cetuximab, we treated 94 patients, with average number of therapy cycle of 5.94.*

Conclusion: *Despite proven benefits of mAbs for many other indications according to FDA, in our Institution (based on the indications approved by Republic Institute of Health Insurance), bevacizumab, and cetuximab are used for colorectal cancer, trastuzumab is only used for breast cancer and rituximab for non-Hodgkin lymphoma. The decrease of the number of ampoules dispensed from our pharmacy and the number of patients in 2011 was caused by tightening the criteria indications by Republic Institute of Health Insurance.*

Key words: *Antibodies, Monoclonal; Neoplasms; Drug Therapy; Antineoplastic Agents*

Arch Oncol 2012;20(3-4):53-6.

UDC: 616-006:615-085(497.113 Vojvodina)"2007/2011"
DOI: 10.2298/AOO1204053J

[1]Depatment for Medical Oncology, Oncology Institute of Vojvodina, Sremska Kamenica, Serbia, [2]Medical Faculty of Novi Sad, Novi Sad, Serbia

Correspondence to:
Marija Jelić, Master of Pharmacy, Oncology Institute of Vojvodina, Put dr Goldmana 4, 21204 Sremska Kamenica, Serbia

marija.jelic_ns@yahoo.com

Received: 26.12.2012
Provisionally accepted: 28.12.2012
Accepted: 29.12.2012

INTRODUCTION

The term targeted therapies refers to treatment strategies directed against molecular targets that are involved in the process of neoplastic transformation. In the second half of the twentieth century, cancer treatment options evolved with more sophisticated selection of targets for cancer therapy, which led to the development of more intelligent drugs directed against these specific targets (1). One group of molecular targeted agents is monoclonal antibodies (mAbs).

The purpose of this study was to show the expenditure of mAbs at the Oncology Institute of Vojvodina from 2007 to 2011. Next, to display the number of patients treated with mAbs, for each indication.

MATERIAL AND METHODS

From 2007, we use software programs Lirpis and LWM for the purposes of monitoring supply, distribution, and drug expenditure at our Institute. These programs were used for collecting data regarding mAbs expenditure during 5-year period, from April 2007 to the end of 2011.

The comments about the situation in our country regarding the indications for mAbs were given with the review on the FDA approvals (Table 1).

RESULTS

The use of mAbs at the Oncology Institute of Vojvodina began in 2005. The first one that became available for the treatment was rituximab, followed by the use of trastuzumab. The expenditure of mAbs during the 5-year period was expressed by the number of ampoules dispensed from hospital pharmacy each year, respectively.

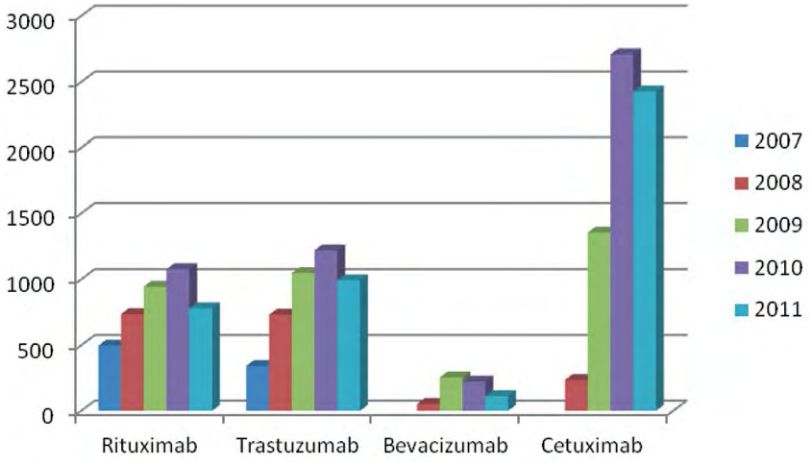

Figure 1. Number of ampoules dispensed from pharmacy each year from April 2007 to 2011

Figure 1 shows the increase in number of ampoules dispensed from the pharmacy from 2007 to 2010, and a slight decrease in 2011 for all monoclonal antibodies.

Figure below shows the total number of patients treated with each mAbs. In addition, it displays number of hospital contacts that include therapy with certain mAbs, necessary for calculating the average number of therapy cycles.

Table 1. FDA approvals for mAbs

	Date of approval	Indication
Bevacizumab	February 2004	First-line treatment of metastatic colorectal cancer
	June 2006	Second line treatment of metastatic colorectal cancer in combination with i.v 5-fluorouracil based chemotherapy
	October 2006	Initial systemic treatment of unresectable, locally advanced, recurrent, or metastatic, non-squamous, non-small cell lung cancer in combination with carboplatin and paclitaxel
	February 2008*	Metastatic breast cancer
	May 2009	Single agent for progressive glioblastoma following prior therapy
	July 2009	Metastatic renal cell carcinoma in combination with interferon alfa
Cetuximab	February 2004	EGFR-expressing, metastatic colorectal carcinoma in combination with irinotecan in patients who are refractory to irinotecan-based chemotherapy
		EGFR-expressing, recurrent metastatic colorectal carcinoma in patients who are intolerant to irinotecan-based chemotherapy
	March 2006	Locally or regionally advanced squamous cell carcinoma of the head and neck (SCCHN) in combination with radiation or as a single agent for the treatment of recurrent or metastatic SCCHN for whom prior platinum-based therapy has failed
	November 2011	First-line treatment of recurrent locoregional disease and/or metastatic SCCHN in combination with platinum-based therapy plus 5-florouracil
	July 2012	First-line treatment of patients with K-ras mutation-negative EGFR-expressing metastatic colorectal cancer in combination with FOLFIRI (irinotecan, 5-fluorouracil, and leucovorin)
Trastuzumab	November 2006	Adjuvant treatment of women with node-positive, HER2-overexpressing breast cancer as a part of a treatment regimen containing doxorubicin, cyclophosphamide, and paclitaxel
	October 2010	For the treatment of HER2-overexpressing metastatic gastric or gastroesophegal (GE) junction adenocarcinoma who have not received prior treatment for metastatic disease, in combination with cisplatin and a fluoropyrimidine (either capecitabine or 5-fluorouracil)
Rituximab	February 2006	First-line treatment of diffuse large B-cell, CD20-positive, non-Hodgkin's lymphoma in combination with cyclophosphamide, doxorubicin, vincristine and prednisone or other anthracycline-based chemotherapy regimens
	September 2006	First-line treatment of patients with low grade or follicular B-cell, CD20-positive non-Hodgkin's lymphoma
	February 2010	Treatment of both previously untreated and previously treated chronic lymphocytic leukemia in combination with fludarabine and cyclophosphamide (FC)
	January 2011	Maintenance therapy for previously untreated follicular CD-20 positive B-cell non-Hodgkin lymphoma who achieve a response to rituximab in combination with chemotherapy

* On November 18, 2011, Food and Drug Administration Commissioner revoked the agency's accelerated approval of the breast cancer indication for bevacizumab because it did not show to provide a benefit.

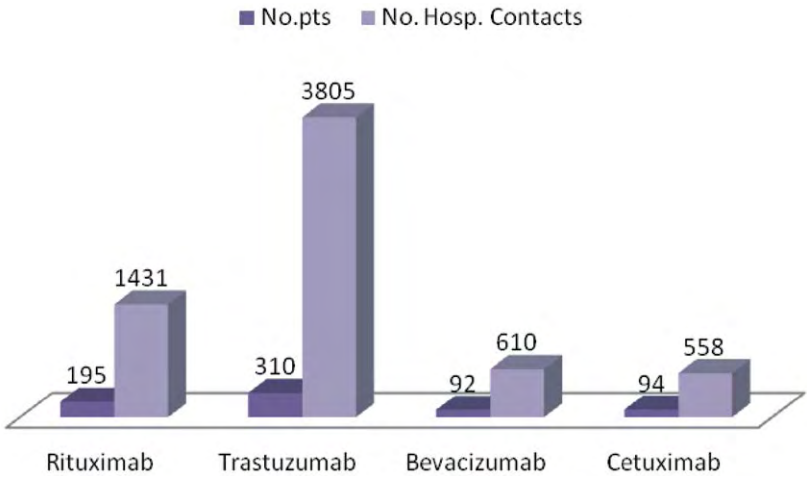

Figure 2. Total number of patients and hospital contacts from 2007 to 2011

Therapy cycles were calculated by dividing the number of hospital contacts that included MA therapy with the number of patients. Results are shown in the Table 2.

Table 2. Number of ampoules, patients, and therapy cycles for the 5-year period

	No of ampoules	No of patients	No. of therapy cycles
Rituximab	4070	195	7.34
Trastuzumab	4341	310	12.27
***Bevacizumab**	1343	92	6.63
***Cetuximab**	7051	94	5.94

*Bevacizumab and cetuximab were not available in 2007. The results are shown from 2008 to 2011.

DISCUSSION

There are three potential approaches to attack a membrane receptor:

- Neutralization of the ligand
- Competitive inhibition of ligand–receptor engagement
- Inhibition of transduction of the signal from the receptor to secondary cytoplasmic messengers (1).

The first target for intervention in a signaling cascade is the neutralization of ligands before they can associate with their receptors. This approach has been successfully validated with bevacizumab, a humanized monoclonal antibody targeting circulating vascular endothelial growth factor (VEGF) (2).

Bevacizumab is derived from the parent murine anti-VEGF MAb (3). It binds to all major human isoforms of VEGF (also known as VEGF-A) (4). Bevacizumab binding to VEGF prevents VEGF from binding to the VEGF receptor (VEGF receptor-1 and VEGF receptor-2) on vascular endothelial cells, thus preventing VEGF-mediated signaling and inhibiting tumor angiogenesis. This ultimately leads to a reduction in microvascular growth, inhibits progression of metastatic disease, and reduces intratumoral pressure, which may improve the delivery of cytotoxic agents (5, 6). Furthermore, in the absence of VEGF signals, endothelial cells become fragile and susceptible to apoptosis. The cells rupture and vessels bleed, resulting in reduced blood flow and vessel regression (7, 8). Bevacizumab has shown benefits in advanced nonsquamous non–small cell lung cancer (NSCLC) in combination with carboplatin and paclitaxel in people who have not received chemotherapy for their advanced disease (9), in patients with metastatic kidney cancer (mRCC) when used with interferon alfa (10), and in glioblastoma (GBM) in adult patients whose cancer has progressed after prior treatment (11, 12). However, in Serbia, bevacizumab is only approved for colorectal, metastatic, potentially resectable cancer, predominant in liver, in the clinical stage IVB or IVC as the first line systemic treatment in combination with chemotherapy until the resectability of metastasis is achieved and with maximum of 10 therapy cycles.
As a second option, direct inhibition of ligand–receptor engagement can be achieved by preventing the binding of the growth factors to their receptors by mimicking the ligand's structure and interfering thus in the ligand–receptor affinity. A proof of this concept is cetuximab, a chimeric antibody against the epidermal growth factor receptor (EGFR) (13). Trastuzumab activity against the HER2 receptor is also a clear, successful approach (14).
Epidermal growth factor receptor (EGFR), a member of the ErbB family of receptors, is relevant in colorectal cancer because the expression or upregulation of the EGFR gene occurs in 60 to 80 percent of cases (15-17). Moreover, expression of the gene is associated with poor survival (18, 19). When inactive, EGFR is a monomer, but when bound by epidermal growth factor or transforming growth factor α (TGF-α), it forms homodimers or heterodimers with another member of the ErbB family of receptors. Dimerization activates the intracellular tyrosine kinase region of EGFR, resulting in autophosphorylation and initiating a cascade of intracellular events (20). The EGFR signaling pathway regulates cell differentiation, proliferation, migration, angiogenesis, and apoptosis, all of which become deregulated in cancer cells (21). Cetuximab, recombinant, human/mouse chimeric IgG1 monoclonal antibody, binds to extracellular domain of EGFR with high specificity and with a higher affinity than either epidermal growth factor or TGF-α, thus blocking ligand-induced phosphorylation of EGFR and activation of receptor-associated kinases, resulting in inhibition of cell growth, induction of apoptosis, and decreased matrix metalloproteinase and vascular endothelial growth factor production. The EGFR is constitutively expressed in many normal epithelial tissues, including the skin and hair follicle. Cetuximab is indicated for colorectal and squamous cell carcinomas of the head and neck (SCCHN) and for both is approved in our country. For metastatic colorectal cancer, it is indicated after the chemotherapy based on oxaliplatin and irinotecan, for tumors with non-mutated K-ras gene, as monotherapy or in combination with irinotecan. For SCCHN it is used if the disease is locally advanced, inoperable, if radiotherapy was not indicated initially, after chemotherapy, in combination with radiotherapy. In addition, if the locally advanced disease is inoperable, cetuximab is used in combination with radiotherapy in patients when platinum-based therapy is contraindicated.
HER2 is a transmembrane tyrosine kinase receptor, which belongs to the family of the EGFR (epidermal growth factor receptor). It is overexpressed in 20%–30% of human breast cancers (22). Its unique feature, which differentiates it from the other members of the family, is the absence of a known ligand. It was reported that HER2 requires HER3 to drive breast cancer cell proliferation (23). Trastuzumab is a humanized mAb of the immunoglobulin G1 type directed against the extracellular portion of HER2 (24). Among proposed mechanisms of action is activation of antibody-dependent cellular cytotoxicity (ADCC) (25-27). ADCC is mainly due to the activation of natural killer cells (NK), expressing the Fc gamma receptor, which can be bound by the Fc domain of trastuzumab. This event activates the lysis of cancer cells bound to trastuzumab. Next, trastuzumab can block the shedding of the extracellular domain of HER2 by inhibiting metalloproteinase activity. Trastuzumab also specifically inhibits phosphoinositide 3-kinase (PI3K) signaling, which in turn leads to inhibition of cell proliferation. Overexpression of HER2 in breast cancer cells is closely associated with increased angiogenesis. One of the trastuzumab mechanisms of action is inhibition of angiogenesis. Cells treated with trastuzumab undergo arrest during the G1 phase of the cell cycle, with a concomitant reduction in proliferation. ToGA study, which was the first randomized trial investigating anti-HER2 therapy in advanced gastric cancer showed that trastuzumab + chemotherapy is superior to chemotherapy alone. Despite the overall survival benefit proven in this study, trastuzumab is in Serbia indicated only for breast cancer (28). It is indicated if there is overexpression of HER2 gene after the adjuvant therapy with anthracyclines, as monotherapy or in combination with taxanes, to 12 months, in node positive and node negative patients with tumors larger then 10mm. For metastatic disease, it is the first line treatment after anthracycline therapy, in combination with taxanes, 6 to 8 cycles, and in progression-free period trastuzumab is given as monotherapy until the progression. For locally advanced breast cancer, it is given in combination with taxane chemotherapy, after the previous sequential use of anthracyclines.
Rituximab is a chimeric antibody in which the variable antigen-binding part (Fab) directed against the CD20 antigen is of murine origin, and the constant part (Fc), important for the activation of human effector functions, is of human origin. The CD20 antigen is expressed abundantly on most normal B cells (but not on stem cells and plasma cells), and, importantly, on more than 90% of B cell lymphomas. It is an antigen that is neither shed nor modulated, making it a very suitable target for antibody therapy (29). Rituximab destroys B-cells by multiple mechanisms including complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity, growth inhibition, and apoptosis (30). Despite proven benefits of rituximab in chronic lymphocytic leukemia (CLL), in Serbia it is approved only for non-Hodgkin lymphoma. It is indicated if the tumor is CD20 positive, for the subtype of diffuse large B cell lymphoma in newly

diagnosed patients, in combination with chemotherapy. Rituximab is also indicated in subtype of follicular lymphoma, both in newly diagnosed and patients in relapse.

CONCLUSION

As shown in the results there was the increase in number of ampoules dispensed from the pharmacy from 2007 to 2010, and a slight decrease in 2011 for all monoclonal antibodies. The decrease of the number of ampoules dispensed from our pharmacy and the number of patients in 2011 is caused by tightening the criteria indications by the Republic Institute of Health Insurance.

Conflict of interest

We declare no conflicts of interest.

REFERENCES

1 Giaccone G, Soria JC. Targeted therapies in oncology. New York: Informa Healthcare USA; 2007.

2 Susman E. Bevacizumab adds survival benefit in colorectal cancer. *Lancet Oncol*. 2005;6(3):136.

3 Kim R. Introduction, mechanism of action and rationale for anti-vascular endothelial growth factor drugs in age-related macular degeneration. *Indian J Ophthalmol*. 2007;55:413-5.

4 Nicholas P, Joel M, Qin R, Ashique R, Michael PR, Ergang S, et al. Binding and neutralization of vascular endothelial growth factor (VEGF) and related ligands by VEGF Trap, ranibizumab and bevacizumab. *Angiogenesis*. 2012;15(2):171–85.

5 Ferrara N, Gerber HP, LeCouter J. The biology of VEGF and its receptors. *Nat Med*. 2003;9:669-76.

6 Lee TH, Avraham HK, Jiang S, Avraham S. Vascular endothelial growth factor modulates the transendothelial migration of MDA-MB-231 breast cancer cells through regulation of brain microvascular endothelial cell permeability. *J Biol Chem*. 2003;278:5277–84.

7 Bergers G, Benjamin LE. Tumorigenesis and the angiogenic switch. *Nat Rev Cancer*. 2003;3:401–10.

8 Carmeliet P. Angiogenesis in health and disease. *Nat Med*. 2003;9:653–76.

9 Maria AB, Clorinda S, Antonio R, Paolo M, Paola CS, Rosario Z, et al. Treatment of advanced non small cell lung cancer. *J Thorac Dis*. 2011; 3(2):122–33.

10 Summers J, Cohen MH, Keegan P, Pazdur R. FDA Drug Approval Summary: Bevacizumab plus Interferon for Advanced Renal Cell Carcinoma. *Oncologist*. 2010;15(1):104-11.

11 Marc CC. Bevacizumab for the Treatment of Recurrent Glioblastoma. *Clin Med Insights Oncol*. 2011;5:117–29.

12 Manfred W, Katrin L. Other Experimental Therapies for Glioma. *Recent Results in Cancer Research*. 2009;171:155-64.

13 Meyerhardt JA, Mayer RJ. Systemic therapy for colorectal cancer. *N Engl J Med*. 2005;352(5):476–87.

14 Brand FX, Ravanel N, Gauchez AS, Pasquier D, Payan R, Fagret D, et al. Prospect for anti-her2 receptor therapy in breast cancer. *Anticancer Res*. 2006;26(1B):715–22.

15 Messa C, Russo F, Caruso MG, Di Leo A. EGF, TGF-alpha, and EGF-R in human colorectal adenocarcinoma. *Acta Oncol*.1998;37:285-9.

16 Porebska I, Harlozinska A, Bojarowski T. Expression of the tyrosine kinase activity growth factor receptors (EGFR, ERB B2, ERB B3) in colorectal adenocarcinomas and adenomas. *Tumour Biol*. 2000;21:105-15.

17 Deschoolmeester V, Baay M, Specenier P, Lardon F, Vermorken JB. A Review of the Most Promising Biomarkers in Colorectal Cancer: One Step Closer to Targeted Therapy. *Oncologist*. 2010;15:699-731.

18 Goldstein NS, Armin M. Epidermal growth factor receptor immunohistochemical reactivity in patients with American Joint Committee on Cancer Stage IV colon adenocarcinoma: implications for a standardized scoring system. *Cancer*. 2001;92:1331-46.

19 Mayer A, Takimoto M, Fritz E, Schellander G,Kofler K, Ludwig H. The prognostic significance of proliferating cell nuclear antigen, epidermal growth factor receptor, and mdr gene expression in colorectal cancer. *Cancer*. 1993;71:2454-60.

20 Klapper LN, Kirschbaum MH, Sela M, Yarden Y. Biochemical and clinical implications of the ErbB/HER signaling network of growth factor receptors. *Adv Cancer Res*. 2000;77:25-79.

21 Ciardiello F, Tortora G. A novel approach in the treatment of cancer: targeting the epidermal growth factor receptor. *Clin Cancer Res*. 2001;7:2958-70.

22 Hudis CA, Trastuzumab — Mechanism of Action and Use in Clinical Practice. *N Engl J Med*. 2007;357:39-51.

23 Holbro T, Beerli RR, Maurer F, Koziczak M, Barbas CF, III,, Hynes NE. The ErbB2/ErbB3 heterodimer functions as an oncogenic unit: ErbB2 requires ErbB3 to drive breast tumor cell proliferation. *Proc Natl Acad Sci USA*. 2003;100:8933–8.

24 Valabrega G, Montemurro F, Aglietta M. Trastuzumab: mechanism of action, resistance and future perspectives in HER2 overexpressing breast cancer. *Ann Oncol*. 2007;18:977–84.

25 Cooley S, Burns LJ, Repka T, Miller JS. Natural killer cell cytotoxicity of breast cancer targets is enhanced by two distinct mechanisms of antibody-dependent cellular cytotoxicity against LFA-3 and HER2/neu. *Exp Hematol*. 1999;27:1533–41.

26 Lewis GD, Figari I, Fendly B, Wong WL, Carter P, Gorman C, et al. Differential responses of human tumor cell lines to anti-p185HER2 monoclonal antibodies. *Cancer Immunol Immunother*. 1993;37:255–63.

27 Clynes RA, Towers TL, Presta LG, Ravetch JV. Inhibitory Fc receptors modulate in vivo cytoxicity against tumor targets. *Nat Med*. 2000;6:443–6.

28 Van Cutsem E, Kang Y, Chung H, Shen L, Sawaki A, Lordick F, et al. Efficacy results from the ToGA trial: A phase III study of trastuzumab added to standard chemotherapy (CT) in first-line human epidermal growth factor receptor 2 (HER2)-positive advanced gastric cancer (GC). *J Clin Oncol*. 2009;27:18.

29 Reff ME, Carner K, Chambers KS, Chinn PC, Leonard JE, Raab R, et al. Depletion of B cells in vivo by a chimeric mouse human monoclonal antibody to CD20. *Blood*. 1994;83:435-45.

30 Bonavida B. Rituximab-induced inhibition of antiapoptotic cell survival pathways: implications in chemo/immunoresistance, rituximab unresponsiveness, prognostic and novel therapeutic interventions. *Oncogene*. 2007;26:3629–36.