Lack of Access to Targeted Cancer Treatment Modalities in the Developing World in the Era of Precision Medicine: Real-Life Lessons From Bosnia

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Patients with cancer in developing and low-income countries have limited access to targeted cancer therapies. The transitional nature of these economies has influenced health care funding, which has resulted in the unavailability of targeted cancer treatments.[1,2] Besides the three studies that will be described here, to our knowledge, no literature exists on the clinical outcome of patients treated with delayed targeted cancer therapy. To raise awareness on the importance of timely targeted cancer treatment, we will discuss three key issues: (1) the low number of targeted cancer therapies for different cancers, (2) the delay in cancer treatment, and (3) the unavailability of cancer diagnostics.

Low Number of Targeted Cancer Therapies for Different Cancers

From our experience in Bosnia, the majority of patients with cancer who require targeted therapy are faced with two options: (1) they never receive the therapy because it is not found on the list of government-reimbursed drugs, or (2) they are put on the waiting lists for one of nine available drugs that are reimbursed. Currently, only nine targeted cancer treatments are available in Bosnia through the Solidarity Fund, a subsidiary of the federal government responsible for the allocation of expensive drugs. The list of targeted treatments, the cancers that they are approved for, and the length of the wait-list for each therapy are listed in Table 1. Funded therapies include imatinib and nilotinib for chronic myeloid leukemia (CML), Philadelphia-chromosome–positive acute lymphoblastic leukemia, and gastrointestinal stromal tumor (GIST); rituximab for chronic lymphocytic leukemia and lymphoma; bevacizumab for colon cancer only (not reimbursed for renal cell carcinoma; Table 2); erlotinib for epidermal growth factor receptor (EGFR)–mutated non–small-cell lung cancer (NSCLC); sunitinib for renal cell carcinoma; sorafenib for hepatocellular carcinoma only (not for renal cell carcinoma; Table 2); everolimus for renal cell carcinoma and breast cancer; and trastuzumab for human epidermal growth factor receptor 2 (HER2)–positive breast cancer. There is no waiting for imatinib, erlotinib, everolimus, and trastuzumab for the indications given previously. The Solidarity Fund was created in 2004, and the list of the nine funded cancer therapies has not been updated in years—the first drug was approved in January 2004 (rituximab), and the last one was approved in December 2013 (everolimus; Table 1).

A recent survey by the European Society for Medical Oncology reviewed the availability of cancer therapies in Europe, with the aim of evaluating the formulary and out-of-pocket costs, as well as the actual availability of the medication (Table 2).[3] From their report, which is updated in Table 2, it is clear that most cancer drugs for melanoma, renal cell carcinoma, NSCLC, metastatic breast cancer, and prostate cancer are not freely available in Bosnia. For example, drugs such as pazopanib, crizotinib, ipilimumab, vemurafenib, and panitumumab are available at all times for patients to pay at full cost (there is no copay through governmental insurance). It is important to note that most people are insured through governmental insurance, and private insurance systems do not function widely in Bosnia. New cancer treatments may be available to some patients through the few clinical trials that are conducted in four clinical centers, in Sarajevo, Tuzla, Banja Luka, and Mostar.

Delay in Cancer Treatment

The waiting lists for targeted cancer therapies have existed since 2004, and depending on the therapy, the wait could be from several months to years. Besides the lack of new cancer treatments, patients who can be treated with the available drugs have to wait for the therapy (Table 1).

Table 1. Targeted Cancer Therapies Available in Bosnia and Herzegovina From 2004 to 2016

Targeted Therapy	Reimbursed for Cancer	Date Therapy Became Available	Wait Time	Molecular Markers Needed for Diagnosis and Follow-Up
Imatinib	CML, Ph+ ALL, GIST	June 2005	1-68 months, from 2005-2013; median wait, 14 months	*BCR-ABL1* molecular testing
Nilotinib	CML, Ph+ ALL, GIST	March 2011	Until December 2013; median wait, 9 months	*BCR-ABL1* molecular testing
Rituximab	CLL, lymphoma	January 2004	Most patients on the waiting list never receive it; < 10% of patients receive it in 3-4 months	
Bevacizumab	Reimbursed only for colon cancer	July 2006	8-12 months	
Erlotinib	Non–small-cell lung cancer	July 2006	No waiting list with detected *EGFR* mutation*	*EGFR*, *KRAS* mutation
Sunitinib	Renal cell carcinoma	July 2008	3-4 months	
Sorafenib	Reimbursed only for hepatocellular carcinoma	April 2012	3-4 months	
Everolimus	Renal cell carcinoma, breast cancer	December 2013	No waiting list (only for renal cell cancer)	
Trastuzumab	Breast cancer	January 2004	No waiting list	*HER2* positivity by IHC and/or FISH/CISH assays†

NOTE. For each targeted therapy, the type of cancer, start of reimbursement, length of wait time, and molecular markers are listed.

Abbreviations: ALL, acute lymphoblastic leukemia; CISH, chromogenic in situ hybridization; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; FISH, fluorescence in situ hybridization; GIST, gastrointestinal stromal tumor; IHC, immunohistochemistry; Ph+, Philadelphia-chromosome–positive.

**EGFR* mutation testing takes up to 2 months to complete.

†Human epidermal growth factor receptor 2 testing is available in all academic centers in the country.

The estimation of the length of the wait time has been based on the Solidarity Fund's committee evaluation, which meets monthly and assigns the targeted therapies to patients after the hematologist/oncologist's application. Patients are placed on the long waiting lists for each drug, which function on a first-come, first-serve basis. Thus, treatment delay is the norm and not the exception. Two country-wide studies in Bosnia and Lithuania have shown the deleterious effects of delayed targeted treatment (imatinib mesylate) for patients with CML.[1,2] CML is a rapidly progressing disease, and 17% of patients in the last 10 years died before receiving the required therapy in Bosnia. For imatinib mesylate, a tyrosine kinase inhibitor (TKI) given to patients with CML and GIST, waiting lists have existed from 2005 to 2013 in Bosnia and Lithuania. In Bosnia, more than 65% of patients with CML received imatinib after a median waiting period of 14 months. Delayed targeted treatment affected significantly all patient outcomes, including survival and cytogenetic and molecular response.[1] At 5 years, the survival rate was 0% for patients who never received TKI (n = 23), 91% for immediate treatment (0-5 months), 81% for patients who waited 6 to 12 months, and 64% for patients who waited > 13 months. After 1 year of therapy, cytogenetic response was achieved in 67% of patients in the immediate imatinib-treatment group, compared with 15% of patients in the group who waited > 13 months.[1]

The Lithuanian study also reported delayed imatinib treatment, where most patients > 64 years of age never received imatinib.[2] Similar to Bosnia, imatinib became partially available in Lithuania in 2005. During the period from 2005 to 2009, imatinib was reserved only for the youngest patients—only 8% of patients > 55 years of age received imatinib. After 2011, all newly diagnosed patients with CML received imatinib as a first-line treatment. However, from 2010 to 2013, 69% of all patients with CML were treated with TKIs.[2]

At present, more than 120 patients with colon cancer are on the waiting list for bevacizumab in the Federation of Bosnia and Herzegovina. Patients with GIST (n = 145) diagnosed in the last 10 years in Bosnia also had to wait for the imatinib treatment (range, 0-67 months; median, 17 months), but their outcome was not affected, probably because of the biology of the disease.[4]

Unavailability of Molecular Cancer Diagnostics

Apart from the delayed therapy caused by the lack of funding, the delay in the targeted therapy for Bosnian patients may be related to the insufficient molecular profiling essays that provide the predictive biomarkers for targeted therapy. Thus,

Table 2. Availability and Cost of Cancer Treatments in Bosnia and Herzegovina

Type of Cancer	Drug	Formulary and Cost	Actual Availability	Solidarity Fund Wait-List
Melanoma	Interferon	Full cost	Available	Not available
	Dacarbazine	Free	Available	Available
	Fotemustine	Not available	Not available	Not available
	High-dose IL-2	Not available	Available	Not available
	TNF	Not available	Not available	Not available
	Temozolomide	Not available	Available	Not available
	Ipilimumab	Full cost	Not available	Not available
	Vemurafenib	Full cost	Available	Not available
	Trametinib	Not available	Not available	Not available
	Dabrafenib	Not available	Not available	Not available
Renal cell	Pazopanib	Full cost	Available	Not available
	Sorafenib	Full cost	Available	Not available (only for hepatocellular carcinoma)
	Sunitinib	Free	Available	3-4 months
	Axitinib	Full cost	Available	Not available
	Everolimus	Free	Always available	No wait
	Temsirolimus	Not available	Never	Not available
	Bevacizumab	Full cost	Available	Not available (only for colon cancer, in which there is an 8- to 12-month wait)
	High-dose IL-2	Not available	Available	Not available
	Interferon	Full cost	Available	Not available
NSCLC	Erlotinib, EGFR-mutated	Free	Available	No wait
	Gefitinib, EGFR-mutated	Not available	Not available	Not available
	Afatinib	Not available	Not available	Not available
	Crizotinib ALK-mutated	Full cost*	Always available	Not available
	Cetuximab	Full cost	Always available	Not available
	Panitumumab	Full cost	Always available	Not available
Metastatic breast cancer	Fulvestrant	Not available*	Available	Not available
	Trastuzumab	Free	Available	No wait
	Pertuzumab	Full cost†	Available	Not available
	TDM-1	Not available	Available	Not available
	Lapatinib	Full cost	Available	Not available
Prostate	Docetaxel	Free	Available	Not available
	Cabazitaxel	Full cost	Available	Not available
	Ketoconazole	Not available	Not available	Not available
	Abiraterone	Full cost	Available	Not available
	Enzalutamide	Full cost*	Available	Not available
	Radium-223	Not available	Not available	Not available

NOTE. The Formulary and Cost column represents the registration and availability of cancer treatments for specified tumors in Bosnia; full cost means that the drug is registered and available but the patient pays the full cost; not available means that the drug is not registered; free means that the drug is completely reimbursed by the government. The Actual Availability column represents actual cost and reimbursement for each therapy; always available means that the drug can be obtained in Bosnia, regardless of the reimbursement policy; not available means that the drug cannot be obtained. The Solidarity Fund Wait-List column represents drugs that can be obtained and reimbursed for the full price for the specified tumors and the length of wait-list. Data for the Formulary and Cost column and Actual Availability column were taken and updated from the article by Cherny et al.[3]
Abbreviations: ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; IL-2, interleukin-2; NSLC, non–small-cell lung cancer; TDM-1, trastuzumab emtansine; TNF, tumor necrosis factor.
*Status changed since the article by Cherny et al was published.[3]
†Under review.

EGFR and *KRAS* testing for NSCLC is performed in one academic center in the country and has been funded by the Roche BiH d.o.o. since 2012. This is the only centralized molecular testing program in Bosnia and Herzegovina, and despite it, the program is not devoid of the inconsistent data caused by both preanalytical and analytical factors.

HER2 testing is performed for all newly diagnosed and recurrent/distant metastatic breast cancers and advanced gastric cancer, as recommended by the most recent guidelines. The testing includes immunohistochemistry (IHC) and in situ hybridization (mainly chromogenic) assays. Although IHC assay is performed in all histopathology laboratories across the country, chromogenic in situ hybridization assays for *HER2/neu* gene amplification evaluation is performed in only three laboratories in the country (two laboratories in the Federation of Bosnia and Herzegovina [Sarajevo and Tuzla] and one laboratory in Republika Srpska [Banja Luka]). The central pathology laboratory in Sarajevo is included in the external quality control assessment for *HER2 t*esting performed by the NordiQC. *HER2* testing and external quality control are in part funded by the local pharmaceutical companies. In 2016, the central pathology laboratory in Sarajevo performed 440 HER2 IHC assays (380 breast and 60 gastric cancer assays) and 55 chromogenic in situ hybridization assays. Overall, HER2 positivity in breast cancer was 18%. Predictive molecular tests for melanoma, colorectal carcinoma, and other cancers (eg, *BRAF, KRAS, MSI*) are not widely available. *ALK* and *ROS* gene testing for NSCLC are not available at all.

The importance of studying the effects of delayed therapy or the lack of targeted cancer therapy in patients transcends the local and individual level and extrapolates to a more global health care issue, because many developing and low-income countries have gradually introduced targeted cancer therapy, but still have patients whose clinical outcome may be affected by the delayed access to the targeted treatment modalities.[1,2,4-6] In Bosnia, the causes could be found in the lack of governmental funding and the lack of unified health policy caused by the complicated political system of postwar Bosnia and Herzegovina. Therefore, the solution to this issue lies in the joint efforts of health care professionals, governmental stakeholders, and patient associations to overcome the present situation and improve both the molecular diagnostics and increase the availability of the targeted cancer treatment modalities.

In conclusion, we have an increasing number of available targeted treatments in the developed world. However, in low- and middle-income countries, we are witnessing an increasing number of patients with cancer[7] that is accompanied by the limited number of targeted therapies and their precision diagnostics. In Bosnia and Herzegovina, only a limited number of targeted cancer treatments are available for reimbursement by the government (Table 2). One reason for this is the unclear application procedure for the introduction of new drugs on the reimbursement list. Also, no clear guidelines and timeframe have been instituted for the reviews of the actual drug lists. In addition, the available cancer medicines are subjected to yearly tender procedures, which are often late and create long delays in availability. In Bosnia and Herzegovina, there is a clear political impact on health policy in cancer medicine because making these drugs available depends on the willingness of the ministries of health to comprehend the importance of optimal cancer treatment. Furthermore, public and health professionals do not exercise the required pressure to start solving the problem.

Thus, we appeal to the researchers, physicians, and public from low-income and developing countries to conduct more systematic studies to highlight the causes and effects of the lack of access to targeted therapy. We hope that the Bosnian experience will initiate global efforts that eventually will enable more access to targeted cancer treatment modalities in the era of precision (personalized) medicine.

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