Challenges in Access to New Therapeutic Agents: Marginalized Patients With Cancer in Pakistan and the Need for New Guidelines

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PURPOSE Cancer care disparities persist among the medically underserved patients with cancer in Pakistan. To determine the access that marginalized patients with cancer have to chemotherapy and newer targeted agents in Pakistan approved by essential medicine list 2017, the barriers that patients face in getting such access, the implications of the barriers for the effectiveness of treatment, and ways of overcoming those barriers, with particular attention to breast cancer (BC), diffuse large B-cell lymphoma (DLBCL), and chronic myeloid leukemia (CML), need to be addressed.

METHODS A cross-sectional survey of 28 private and public cancer centers targeting more than 50% of patients with cancer for year 2018 was conducted with focus on access to optimal therapy for BC, DLBCL, and CML. To assess the impact of socioeconomic status on the effectiveness of treatment, patients were categorized into three main income groups—low, middle, and high according to gross domestic product per capita on the basis of which some patients were categorized as economically marginalized. Differences in quality of care in public and private sector hospitals were assessed by optimal delivery and completion of chemotherapy on the basis of international guidelines. Access to optimal dose and timings of targeted therapies were determined.

RESULTS In our marginalized patients, 30%-40% received optimal basic chemotherapy for BC and DLBCL. Less than 10% of patients with human epidermal growth factor receptor 2–positive BC completed 17 cycles of trastuzumab within 12 months. For DLBCL, hardly any patients received concurrent rituximab with chemotherapy for six cycles. Dose delays, modifications, and abandonment of treatment occurred in approximately 50% of the marginalized patients. In patients with CML, the compliance to imatinib/nilotinib was 85%.

CONCLUSION Significant barriers exist in providing optimal basic and targeted therapies to our indigent patients despite government funding and availability of access programs.

INTRODUCTION

By 2040, the relative magnitude of increase in cancer incidence among transitioning/emerging economies or low- and middle-income countries (LMICs) will be 64% with a cancer mortality of 58.3%. Several reasons account for the high mortality rates including improved life expectancy, fewer resources allocated to cancer, lack of cancer registries, and cancer control programs. Other important risk factors include financial constraints, less access to health services, illiteracy, and use of cheaper alternative medicines resulting in high mortality rates. Patients with cancer in LMICs have less access to health services, and within countries, patients with low socioeconomic status have even less access to health care, leading to delayed/not obtaining health care, advanced disease, therefore higher health care costs, lost income, and thus high mortality rates. With limited or no access to health insurance, indigent patients delay or simply not pursue cancer treatment. Premature mortality and morbidities in younger patients, therefore, have a significant economic impact because of loss of years of productivity.

Pakistan has approximately 178,388 new cancer cases and a mortality of 118,442 each year. The annual population growth rate is 2.4%. Breast cancer (BC) is the most common female cancer, and non-Hodgkin lymphoma (NHL) is the third most common male malignancy in Pakistan. Chronic myeloid leukemia (CML) is uncommon, but no treatment options exist except for targeted therapies.

Pakistan is on the lower scale of medium human development index countries, with a gross domestic product per capita of 1,222 US dollars (USD). Approximately 40% of the population lives in multidimensional poverty.
Health care accounts for a meager 3.2% of total public expenditure, and a major portion of this allocation is spent on infectious diseases and maternal child health. Cancer, therefore, is a neglected problem in Pakistan. In particular, poor patients with cancer are at a consistent disadvantage. Inequalities in access to quality cancer care among marginalized patients with cancer in Pakistan are due to several reasons, which include financial constraints, late diagnosis, poor access to high-quality treatment, fragile/fragmented health care systems, and social inequalities. Nearly 70% of patients with cancer are treated in the public sector hospitals. When funds are available, basic cancer drugs are dispensed free of cost to indigent patients in public hospitals, but the burden of supportive care and all other expenses are borne by the patient. In the private sector, all expenses are out-of-pocket expenditures: 10%-15% of such patients are covered fully/partially by their insurance.

In LMICs, cancer treatment follows evidence-based guidelines from the high-income countries, stretching already constrained health resources. The advent of novel therapies, such as checkpoint inhibitors, targeted therapies, and CAR-T cells, is a new generation of cancer treatments in the high-income countries. The development of imatinib for CML, trastuzumab for human epidermal growth factor receptor 2 (HER2)–positive BC, and rituximab for B-cell lymphomas has been considered among the greatest breakthroughs in cancer care in the last few decades. Unfortunately, these targeted treatments are extremely expensive and out of reach for a majority of patients living in the LMICs. To a lesser extent, health care disparities also exist in high-income countries for access to these expensive cancer therapies.

In this study, we explored the current status of cancer care in Pakistan especially among patients categorized as marginalized patients with cancer. In this study, we explored the current status of cancer care in Pakistan especially among patients categorized as marginalized patients with cancer. In this study, we explored the current status of cancer care in Pakistan especially among patients categorized as marginalized patients with cancer. In this study, we explored the current status of cancer care in Pakistan especially among patients categorized as marginalized patients with cancer.

METHODS

Study Design

In Pakistan, a total of 49 institutes (36 government and 13 private) provide treatment to patients with cancer. The study was conducted in Pakistan where patient administrative data are not generally recorded and retained especially in public sector hospitals. We, therefore, designed a survey to get the best possible information under the circumstances. We defined marginalized patients as those falling in the lowest stratum of the middle-income group and in the lowest income group. Marginalized patients were defined as patients living either in multidimensional poverty or belonging to the lowest stratum of the middle-income group.

Survey

The survey was conducted in 28 major institutes, which treat more than 50% of marginalized patients. The 28 institutes covered all four provinces. These institutes were identified as treating more than 500 new cancer cases annually and having senior oncologists serving in their respective institutes for a minimum of 5 years. The data were gathered from senior oncologists in the hospitals treating patients with cancer. Official records were not requested because of lack of individual patient data, red tape, privacy issues, and the experience that formally written replies take too long. These estimates were the best that we could obtain in the prevailing circumstances in Pakistan.

CONTEXT

Key Objective
To determine the accessibility of essential targeted therapies to marginalized patients in Pakistan, a low- and middle-income country.

Knowledge Generated
Less than 10% of the marginalized population has access to optimal essential targeted therapies in human epidermal growth factor receptor 2–positive breast cancer and B-cell non-Hodgkin lymphoma.

Relevance
The inferior progression-free survival and overall survival in human epidermal growth factor receptor 2–positive breast cancer and B-cell non-Hodgkin lymphoma are related to poor access to essential targeted therapies. Efforts by government and health care providers are essential to improve access to these drugs.
We designed our survey to answer five different overarching questions on percentage of patients receiving optimal systemic and targeted therapies for early BC stage I-III, diffuse large B-cell lymphoma (DLBCL), and CML in three different resource settings. Percentages of patients completing optimal basic and targeted therapies within these resource settings were obtained. Reasons for delay/dose modifications and discontinuation were sought. Access to targeted therapies, including identification of reasons for delay/discontinuation of therapy, was obtained. Differences in quality of care delivered in public and private sector hospitals were assessed by optimal delivery and completion of chemotherapy on the basis of international guidelines.

**Access Programs**

In Pakistan, there are three patient access programs available for HER2-positive BC, B-cell NHL, and CML. For the Roche Access Program (UNMOL) in public sector hospitals, the government usually provides only five cycles of trastuzumab for patients with HER2-positive BC. The remaining five cycles are supplied by Roche. Basically, all patients receive a total of only 10 cycles of trastuzumab. A similar program is in place for rituximab except here the government purchases three cycles and Roche provides the other three cycles. For the patient to qualify for government support for targeted therapies in public hospitals, at least 2-3 months are required because of logistics, administrative issues, and verification procedures, so treatment delays occur frequently.

On the other hand, treatment of patients in the private sector is not covered by the government. The patient purchases trastuzumab/rituximab for one cycle, and Roche provides the next cycle free.

Novartis provides imatinib and nilotinib through the Oncology Patient Access Program, Pakistan. All newly diagnosed patients with CML are enrolled in the program and receive both the drugs totally free of cost at designated public hospitals providing treatment for CML. Imatinib and nilotinib are purchased by the government for 3 months annually.

Information on patient number for year 2018 was obtained from patient access programs from Roche and Novartis.

**Socioeconomic Status**

On the basis of most recent data, Pakistan’s population is 215.3 million and its gross domestic product per capita per year in current US dollars is USD 1,222. The average household size according to the 2018-2019 Household and Expenditure Survey is 6.24, and the average urban household is 5.97. The total national income is distributed as follows: the upper 20% of households have 40% of the wealth, the middle 40% have 37% of the wealth, and the bottom 40% have 23% of the wealth.25

For illustrative purposes, we can deduce the following indicative comparative data using an average household size of 6.26

From the above data, the average monthly per capita income per Pakistani household is USD 102. On the basis of the income distribution, the average monthly household incomes of the upper, middle, and lower social strata are USD 1,224, USD 564, and USD 360, respectively. These data are summarized in Table 1. The lowest income stratum is considered to be living below the multidimensional poverty line and is referred to as marginalized in this study.

The cost of cancer treatment is very high, often exceeding the total household income of patients. We have arbitrarily chosen 10% as a relatively high allocation of monthly household income that can be devoted to cancer care on a sustained basis given all other essential household expenditures.27 The motivation is to show that even with this high allocation, the cost of cancer is not sustainable over extended periods for most households. It is true that families often spend more than this by borrowing or selling assets, but such expenditures are not sustainable over time.

We calculated prices for the drugs and converted all estimates into the USD (1 USD = 170 Pakistani Rupee).

**RESULTS**

The response to our survey was 100%. Public sector hospitals receive regular annual allocation of funds from the government for cancer treatment to cover basic first- and second-line cancer therapy. The funds for cancer treatment are insufficient to treat the rapidly growing number of patients with cancer especially those requiring targeted therapies, which are, therefore, provided by Pakistan Bait-ul-Maal (autonomous body for poverty alleviation by the Government of Pakistan). Other irregular sources for funds include Zakat (obligation of wealthy Muslims to pay for charitable causes) and various other philanthropic donations.

The percentage completing rate for the regimens described below are the pooled data from all institutes to whom survey was sent. The information on treatment delays in public sector hospitals for targeted therapies is due to the standard operating procedures across all public sector hospitals where trastuzumab/rituximab is subsidized by the government.

**Breast Cancer**

In 2018, a total of 1,800 patients with HER2-positive BC applied for the Roche access program. Table 2 depicts the average cost of chemotherapy drugs and supportive care medicines for BC only across all public and private sector hospitals.

Subsidies by the government summarized in Table 2 are only for patients treated in public sector hospitals. Despite subsidies by the government for our indigent patients treated in public sector hospitals, even if the government subsidizes basic cancer treatment of doxorubicin and cyclophosphamide × 6 cycles completely, only 30%-40% complete optimal therapy. If taxanes are added, the
number of patients completing treatment falls to 20%-25%. Optimal treatment with chemotherapy and trastuzumab is completed in only 10%. Dose modifications and therapy delays for basic chemotherapy regimens were frequent because of lack of availability of chemotherapy medicines, comorbid conditions, financial constraints, and expensive supportive care.

Our survey revealed payments for trastuzumab by the government. The average delay was 6-8 weeks because of procedural issues in procurement; as a result, completion of 12 cycles took 18-24 months. Less than 10% of the patients completed 12 months of trastuzumab, with 20%-30% completing 6 months of therapy, whereas the remaining patients abandoned their therapy.

In private sector hospitals, catering to the remaining 30% of patients with cancer, there are no government subsidies. Out-of-pocket expenditures are incurred in approximately 85% of patients, and the remainder is covered by insurance. Despite the lack of subsidies, the number of patients completing therapy with doxorubicin and cyclophosphamide approaches 90%. With the addition of taxanes, 50%-60% complete treatment in the middle-income group and nearly 90% in the upper-income group. When trastuzumab is added to the regimen for HER2-positive BC, optimal treatment is completed in 40%-50% in the middle-income group and approximately 90% of patients in the upper-income group complete treatment on time.

Table 3 shows that optimal delivery of trastuzumab varies markedly according to socioeconomic status, with optimal treatment being completed in only 10% in our marginalized population, compared with 90% in the high-income group.

**TABLE 2.** Cost of Treatment of Early Breast Cancer

| Chemotherapy Drug | Expenditure on Health (USD) | Cost of T/M and Supportive Care Monthly (USD) | Subsidy by Government Monthly (USD) | Outcome Completion of Therapy |
|-------------------|-----------------------------|---------------------------------------------|------------------------------------|-----------------------------|
| Chemotherapy in early BC in low-income patients | | | | |
| AC                | $36                         | $177                                       | $141                               | 30%-40%                     |
| AC plus taxol × 12 | $36                         | $211                                       | $175                               | 20%-25%                     |
| AC plus taxol plus trastuzumab × 17 | $36                         | $1,083                                     | $1,047                             | < 10%                       |
| Chemotherapy in early BC in middle-/high-income patients | | | | |
| AC                | $56/122                     | $177                                       | No subsidy                         | 70%-80%/> 90%               |
| AC plus taxol × 12 | $56/122                     | $211                                       | No subsidy                         | 50%-60%/> 90%               |
| AC plus taxol plus trastuzumab × 17 | $56/122                     | $1,083                                     | No subsidy                         | < 40%-50%/85%-90%           |
| Chemotherapy in DLBCL in low-income patients | | | | |
| CHOP × 6          | $36                         | $135                                       | $99                                | 35%-40%                     |
| R-CHOP × 6        | $36                         | $800                                       | $764                               | < 10%                       |
| Chemotherapy in DLBCL in middle-/high-income patients | | | | |
| R-CHOP × 6        | $56/$122                    | $800                                       | No subsidy                         | > 90%                       |

Abbreviations: AC, doxorubicin plus cyclophosphamide; BC, breast cancer; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisolone; DLBCL, diffuse large B-cell lymphoma; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone; USD, US dollars.

**Diffuse Large B-Cell Lymphomas**

In 2018, 800 patients with DLBCL applied for rituximab through the Roche access program. The results from the survey are summarized in Table 2. Chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisolone alone for six cycles was completed in nearly 50% of the marginalized patients with DLBCL. Again, procurement delays and bureaucratic hurdles by the government were common, leading to an average delayed start of rituximab by 6-8 weeks. The results from our survey revealed that rituximab was usually started after cycle 3. Moreover, there is uncertainty regarding the number of cycles given, but approximately 60% of patients received 2-3 cycles, 30% completed rituximab as single agent over 8-12 months, and 10% abandoned therapy.

On the other hand, more than 90% of patients from the middle and upper class treated in private sector hospitals completed their six cycles on time.

**Chronic Myeloid Leukemia**

A total of 8,500 patients with CML are currently receiving therapy with imatinib/nilotinib. Table 3 shows that...
In Pakistan, several factors are responsible for delay in timely cancer care, resulting in suboptimal outcomes and high mortality rates even when subsidies for basic cancer therapies are available.29 Our survey revealed that non-compliance and incomplete cancer therapies and subsequent abandonment of therapies in indigent patients are common. Reasons include increasingly burdensome out-of-pocket expenditures, which include laboratory/radiology investigations, supportive cancer therapies, lack of nutritional support, and costs of other comorbid conditions. Illiteracy, use of alternative medicines, loss of wages, and difficulties in access to cancer centers among the poor patients further increase noncompliance.4,30

Public sector hospitals in LMICs are not equipped to deal with high burden of cancer, thus affecting outcomes. Overcrowding, limited working hours, and overburdened physicians, which lead to long waiting times, and lack of care coordination are frequent.5-7 Limited and poorly allocated budget is a major hindrance to optimal care, leading to less than optimal delivery of cancer therapies, potential wastage, and inferior outcomes with targeted treatment. Despite the availability of chemotherapy and targeted therapies in public sector hospitals, the estimated magnitude of outcomes differs markedly from private sector hospitals.29 Thus, large inequities exist within our country for cancer treatments.

Catastrophic out-of-pocket spending for cancer care in Pakistan pushes 50%-90% of patients in the lower and lower middle-income group into poverty. A study conducted in Aga Khan University, Karachi, in a tertiary care private cancer center found that of patients receiving chemotherapy for breast and head and neck, 42% experienced a significant financial burden and 27% experienced an unmanageable financial burden.31

Rajpal et al in their cross-sectional survey in India revealed that out-of-pocket expenditure for cancer is highest for any ailment, in excess of 20% of annual per capita household expenditure. Another cross-sectional survey reported that 60 million people in India are pushed below the poverty line every year because of treatment costs associated with cancer in their families.31,32

Simply put, the existing international guidelines are not working in Pakistan. Our indigent population is not completing optimal cycles of expensive targeted therapies, thus wasting resources at both government and patient levels. The outcomes of incomplete therapies are unknown. However, the targeted program for CML has been successful as compliance is more than 85% with excellent outcomes similar to that reported in the developed countries because of prior purchase of drugs by the government.23

Our policy makers should include all stakeholders involved in delivering cancer care and ensure and prioritize these drugs, which have been transformational for HER2-positive BC, B-cell lymphomas, and CML. It is essential to make them affordable and accessible for optimal and timely care to our patients. Resources should be directed and limited to drugs used in curative settings and not on expensive medicines, which have modest outcomes.

With our finite resources, urgent reforms require that government involves all stakeholders for prioritizing drugs according to evidence on outcomes and address affordability for our indigent population. The efficacy and
outcomes of access programs must be judiciously evaluated and improved for our patients to receive optimal benefits of these expensive treatments.33-35 Judicious and rational use of our meager resources is essential as more and more targeted therapies are being approved in cancer care. For these, evidence-based guidelines specific to an LMIC context need to be developed. PERSEPHONE and PHARE trials looked at 6 months of trastuzumab versus 12 months for HER2-positive BC.36,37 Evidence from the two trials is conflicting, but there are minor differences in the 4-year disease-free survival with less toxicity and lower costs. Tannock in his recent article has suggested a utilitarian approach of near equivalence, so we can reach a greater number of patients with more effective therapies to increase access and reduce financial toxicities.38 This is especially pragmatic for the marginalized patients in LMIC, and we should be prepared to accept these challenges. Similarly, for CML, we need to put eligible patients off therapy on treatment-free protocols.39

It will take further research to chart those guidelines in full, but our work does establish certain principles. First, it is extremely important to determine the outcomes in our patients where therapies are delayed or abandoned to prevent current inefficiency, waste, and loss of efficacy of these expensive drugs. Second, we need to address cancer as a public health issue. This means strengthening effective coordination among various stakeholders to create early detection mechanisms, cancer registries, functional cancer control programs, institutional capacity building, identification and eradication of preventable and contributory causes of cancers, and decisive leadership. Guidelines informed by these principles will differ from those in high-income countries, but they will prove to be more effective in LMICs.34,40

One of the major limitations of our study is that our data are the impression of physicians treating these cancers. However, the acknowledgment of the difficulties and hurdles faced by the physicians were universal in all public sector hospitals.

We hope that addressing these specific barriers is crucial to informing guidelines specific to LMICs, which will result in more effective public health policy than guidelines transplanted from a completely different socioeconomic context.

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AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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