The Financial Toxicity of Advanced Hepatocellular Carcinoma Treatment in Low Middle-Income Countries.

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Abstract

Advanced Hepatocellular carcinoma (HCC) is no longer a terminal illness. This change was mainly attributed to the development of new treatments including tyrosine-kinase inhibitors (TKIs), vascular endothelial growth factor (VEGF) inhibitors and immune checkpoint inhibitors (ICPIs) but the financial toxicity of treating advanced HCC is of a major concern specially in low middle-income countries (LMICs) where the patients are still battling for their most basic rights. Most of advanced HCC patients in LMICs have very limited accessibility to the new treatments including ICPIs. Searching for out of the box solutions to improve access to treatments -mainly ICPIs- is an utmost necessity for LMICs advanced HCC patients.

Keywords: Advanced Hepatocellular carcinoma , Immune checkpoint inhibitors, Low middle-income countries, Financial Toxicity

Introduction

Primary liver cancer (PLC) is the sixth most prevalent malignancy across the globe, it is considered among the top five solid tumors with high mortality rate (1). PLC is the third highest cause of cancer-related mortality with 8.2% of all cancer-related deaths in 2020 (1). In low- and middle-income countries (LMICs), the number of new cancer cases has grown with a 1.2 million increment during the six years spanning from 2012 to 2018, while the number of deaths caused by cancer has grown from 5.3 million to 6.7 million during the same period (2,3). The World Health Organization (WHO) estimated that in 2020 there was globally around 906,000 new cases of PLC with almost 90% mortality rate (1). HCC is the most prevalent form of PLC and constitute a significant source of mortality and economic burden worldwide, particularly in LMICs (4).

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In a recent global study, 5% of cancer-related disability-adjusted life years (DALYs) are attributed to liver cancer (5). PLC is most common in Asia and West Africa and for both cancer incidence and mortality in Mongolia, Cambodia and Egypt (1). Worth mentioning that all these countries belong to LMICs according to the World Bank classification (6). The financial toxicity of treating advanced HCC is troublesome for every nation even those with high-income, but of a major concern in LMICs where patients are still battling for even the most basic rights.

Risk factors for developing HCC

Chronic Hepatitis B virus (HBV) infection, chronic Hepatitis C virus (HCV) infection, high alcohol consumption, obesity, aflatoxin-contaminated foods, smoking and type 2 diabetes are the primary risks for developing HCC (7). Nearly 25% of chronic HBV-infected people may develop HCC and perish as a result (8). This is especially worrisome for LMICs in West Africa, where HCC is a leading cause of premature mortality (9). Improved access to screening and vaccination programs may reduce HBV incidence, however there are no such programs in West Africa (9). Chronic HCV infection with cirrhosis account for nearly 7% of global HCC incidence and it is the most prevalent cause of HCC in North and South America (10). HCV incidence in Egypt fell between 0.8 to 6.8 per 1,000 person-years (11).

Treatment options of advanced HCC

The choice of advanced HCC treatment depends mainly on performance status, Child-Pugh score, baseline Alpha Fetoprotein (AFP) level and above them all, the ability of the patient to afford the cost of these treatments. Since 2008, Sorafenib was the only available treatment for patients with advanced HCC (12). However, new options including vascular endothelial growth factor (VEGF) inhibitors, newer tyrosine-kinase inhibitors (TKIs) and immune checkpoint inhibitors (ICPIs) have demonstrated superior efficacy (13). First line options include atezolizumab in combination with bevacizumab or lenvatinib monotherapy or sorafenib or most recently durvalumab with or without tremelimumab. While second line options include nivolumab in combination with ipilimumab as opposed to various monotherapy options including regorafenib, ramucirumab, cabozantinib, sorafenib or Lenvatinib if not used in first line (14).

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Pembrolizumab or nivolumab monotherapy can be considered as option only in certain circumstances in the second line settings as category 2B level of evidence (14).

Does HCC survival correlate with income?

Despite the fact that survival from PLC remain poor even in high income countries; patients diagnosed with PLC in LMICs have a significantly worse 5-year survival rate.

In Uganda (3.2%) and Gambia (3%) than they do in Denmark (9%) and USA (14.8%) (15). Moreover, low-income and rural-neighborhood patients had advanced HCC tumors and higher mortality. These disparities likely reflect suboptimal care, especially in HCC surveillance (16). Another study concluded that poverty and limited access to healthcare may increase the likelihood of developing HCC and shorten the patients' OS time (17).

Financial toxicity of advanced HCC treatment.

The exorbitant cost of cancer treatment may obstacle patients' access to proper care (18). Multiple LMICs devote between 4 and 7 percent of their gross domestic product (GDP) to healthcare, which is generally insufficient to cover even the most basic cancer care (19). The vast majority of cancer patients in LMICs are unable or unwilling to pay for their holistic care. Moreover, in most LMICs, health insurance does not exist (20). Lack of health insurance, lower income, unemployment and younger cancer diagnosis predicted severe financial burdens (21,22). Most of advanced HCC patients in LMICs have very limited accessibility to the new treatments including ICPIs. In a recent real world study conducted in India , it was found that among all patients who were indicated to received ICPIs (9610 Patients), only 1.6 % (155 patients) actually received ICPIs (23).

Moreover, according to the world bank data, the out-of-pocket expenditure (% of current health expenditure) in LMICs is 35.25% on average , reaching a highest percentage of 79.30% in Afghanistan, 64% in Cambodia, 63% in Egypt, 38% in Uganda and 23% in Gambia (24). Meaning that due to the lack of insurance or governmental copayment, the patients must pay for their health care cost out of their own pocket.

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When it comes to HCC ; the median overall direct cost (regardless of stage or treatment) per patient per a year was $176,456 and each patient is predicted to incur indirect expenses of $3553 due to lost productivity (25).

The average wholesale direct costs of ICPIs used in advanced HCC management were extracted in US dollars from RED BOOK online (26) (Table 1) and were as follows: $11818.37 for atezolizumab, $13796.7 for durvalumab, $2821.3 or $4231.9 or $8463.88 for nivolumab (different dose ranges available), $38593.61 for ipilimumab and $12820.22 or $25640.44 for pembrolizumab (different dose ranges available). The meeting of the 23rd WHO expert committee on the selection and use of essential medicines concluded against listing ICPIs as essential medicines. The committee believed that the benefit-to-harm ratio of ICPIs was favorable, however, listing was not suggested because these medications are extremely expensive in many disease contexts at their current pricing (27).

Leaving no one behind

Searching for out of the box solutions to improve access to treatments -mainly ICPIs- is an utmost necessity for LMICs advanced HCC patients. Dose rounding was proven to be a successful method for waste and cost reduction in oncology care (28). In case of weight-based dosing for nivolumab and ipilimumab ; dose rounding within 10% of the ordered doses is expected to substantially reduce the cost and drug waste without impact on medications effectiveness (28). Vial sharing is another strategy to reduced waste and improve cost saving particularly in large or publicly funded institutions (29). Using weight-based dosing strategies instead of fixed dose in combination with vial sharing was also proven to provide cost saving in the case of pembrolizumab and nivolumab, these two strategies saved almost 1.5 million US dollars over only 4 months (30). A study conducted in Taiwan found that giving pembrolizumab with a dose of 1.8 mg/kg achieved similar OS when compared with standard 200 mg every 3 weeks (31). Freshwater et al performed budget impact simulation of pembrolizumab using weight-based dosing (2 mg/kg) compared to fixed 200 mg dose, they found that using the 2 mg/kg dosing produced annual savings of around $0.825 billion (32).

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There is a wealth of evidence suggesting that ICPIs can achieve considerable activity at doses far below those currently approved (33). These evidence are supported by preclinical data suggesting that programmed death-1 (PD-1) receptor occupancy was achieved at very low doses; 90% of PD-1 receptors was saturated at 0.5 mg/kg pembrolizumab, 3 mg/kg avelumab, 4 mg/kg atezolizumab and totally saturated at 0.3 mg/kg durvalumab and 0.3 mg/kg nivolumab (34–37). Moreover, the trough concentration (Cmin) using approved dose (1200 mg) of atezolizumab is 20 times higher than the Cmin achieved using 3 mg/kg in the preclinical trial (35,38,39).

Using a fixed lower nivolumab dose of 20 mg or 100 mg every 3 weeks compared to standard 3 mg/kg biweekly; Yoo et al showed that among 47 non-small cell cancer (NSCLC) patients using low dose along with extended frequency achieved better objective response rate than standard approved dose and frequency (40). Similar results using 100 mg or 140 mg nivolumab were proven by Zhao et al in renal cell carcinoma patients (41). In a phase 2 trial of melanoma patients using fixed low dose 10 mg of adjuvant nivolumab for one year was shown to be an efficient and financially advantageous alternative compared to conventional dosing (42). Pembrolizumab was also tested in 114 advanced NSCLC patients using low fixed dose of 100 mg and showed no differences in OS or PFS compared to standard pembrolizumab dosing (43). Not only can ICPIs be effective when used in lower doses but also when used with extended frequencies and for shorter time than approved legalization. Real world data from a LMIC confirm that shorter course (median of 3 months only) of ICPIs achieved comparable safety and efficacy as conventional treatment regimen (44). Taking all these discussed considerations together A. Patel and his colleagues proposed off label dosing and frequencies for pembrolizumab (1 mg/kg every 6 weeks), nivolumab (0.6 mg/kg every 4 weeks) and atezolizumab (2 mg/kg every 6 weeks) and with this strategy there was cost reduction by 86%, 93% and 95% enough to treat 7, 14 and 21 additional patients respectively (45).

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Outstanding question

With the availability of different treatment options showing OS benefits for previously incurable disease such as advanced HCC; the goal is to have equal access for these medications -such as ICPIs- with no discriminations among nations based on income. Many suggested steps, if adopted globally can improve access to ICPIs. These steps include dose rounding, vial sharing, lower dosage, extended frequencies and shorter ICPIs treatment courses. Additional research should be encouraged to address this unmet need, allowing more patients in LMICs to gain access to these vital treatments.

Table 1: The average wholesale direct cost of ICPIs used in advanced HCC.

Drug name	Doses used in HCC	Place of therapy	Available strength	average wholesale price (USD)	Average direct cost per cycle (USD)	Remarks
Atezolizumab	1200 mg	1st line	840 mg [a]	8272.86	11818.37	Every 3 weeks in combination with bevacizumab
			1200 mg	11818.37		
Durvalumab	1500 mg	1st line	120 mg [b]	1103.74	13796.7	Every 4 weeks, either in combination with tremelimumab or monotherapy
			500 mg	4598.90		
Tremelimumab	300 mg	1st line	NA	NA	NA	Used for a single dose of tremelimumab in combination with Durvalumab every 4 weeks
Nivolumab	1 mg/kg	2nd line	40 mg	1410.65	* 2821.3	Every 3 weeks in combination with ipilimumab for 4 cycles
			100 mg	3526.61		
	240 mg		240 mg	4231.9	4231.9	Monotherapy every 2 weeks
	480 mg		480 mg	8463.88	8463.88	Monotherapy every 4 weeks
Ipilimumab	3 mg/kg	2nd line	50 mg	9648.43	*38593.61	Every 3 weeks in combination with nivolumab for 4 cycles
			200 mg	38593.61		
Pembrolizumab	200 mg	2nd or 3rd line	100 mg	6410.11	12820.22	Every 3 weeks
	400 mg				25640.44	Every 6 weeks
a & b: This dose is not used for advanced HCC, * Dose based on average adult weight of 60 kg, NA : details are not available in RED Book						

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Declarations

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