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Regorafenib or Cabozantinib in second or subsequent lines after Sorafenib in advanced hepatocellular carcinoma. Which way to chose?

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Abstract

The aim of this paper is to assess the cost-effectivess of regorafenib and cabozantib in the treatment of advanced hepatocellular carcinoma (HCC) after sorafenib. Pivotal phase III randomized controlled trials (RCTs) were considered. Incremental cost-effectiveness ratio (ICER) was calculated for both treatments. Two phase III RCTs, including 1274 patients, were considered. Regorafenib resulted the less expensive, with 2771 € per month overall survival (OS)-gained versus 5309 € of cabozantinib. Combining pharmacological costs of drugs with the measure of efficacy represented by the OS, regorafenib is a cost-effective for the treatment of advanced HCC after sorafenib.

Introduction

Recently, the introduction of cabozantinib, a tyrosine kinase inhibitor, offered a therapeutic possibility beyond the first or subsequent-line for patients affected by advanced hepatocellular carcinoma (HCC) in progression after sorafenib, with the improvement in clinical outcomes and prolonged survival [1]. This therapeutical option in this setting of advanced HCC adds to regorafenib, a small-molecule multikinase inhibitor, that improved overall survival (OS) in the pivotal phase III randomized controlled trial (RCT) [2]. The introduction of these active new agents raises the main problem of pharmacy costs increase. The aim of this paper is to assess the cost-effectiveness of regorafenib and cabozantib in the treatment of advanced HCC.

Materials and methods

Pivotal phase III RCTs of regorafenib and cabozantinib in the treatment of advanced HCC after sorafenib in second or subsequent lines were considered. Incremental cost-effectiveness ratio (ICER) was calculated as the ratio between the difference of the costs in the intervention and in the control groups (pharmacy costs) and the difference between the effect in the intervention and in the control groups (OS). The costs of drugs are at the Pharmacy of our Hospital and are expressed in euros (€), updated to June 2020. Calculations were based on an "ideal patient" (BSA 1.8 sqm; weight 70 Kg). The dosage of drugs were considered according to those reported in each RCT. We assumed the following costs for each month of therapy: regorafenib= 1940 € (at the dose of 160 mg/daily for the first 3 weeks of each 4-week cycle), cabozantinib= 2920 € (same price for 60 mg, 40 mg and 20 mg). European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) [3] was applied to the above RCTs to derive a relative ranking of clinical benefit [4].

Results

Two phase III RCTs, including 1274 patients, were considered. The main reported outcomes of the analyzed phase III RCTs are reported in table 1. ESMO-MCBS (Table 1) reached grade 3 for RESORCE trial [2] and grade 2 for the CELESTIAL trial [2]. Regorafenib resulted the less expensive, with 2771 € per month OS-gained (Table 1).

Discussion

Two main variables are able to condition pharmacy costs: the efficacy of treatment and the price of drugs. The first variable is related to the patient's inclusions criteria and we know that results from RCTs could be not representative of daily clinical practice (that is of patients treated outside such trials). The price of drugs is the second strong variable [5,6].

In addition, the annual perspective of the annual cost of treatment wit regorafenib (33 252 €) is in line with those reported in literature, that found a favored implementing intervention for thresholds of less than $61,500 (57 138 €) per life-year gained [7], differently from cabozantinib (63 708 €).

However, to our knowledge, this is the first time an analysis of the pharmacological costs of advanced HCC treated with regorafenib or cabozantinib after sorafenib is linked to OS.

The results become even more interesting if we consider that 51% of patients in the RESORCE trial [3] and 62% in the CELESTIAL trial [2] have reduced the full dose of regorafenib and cabozantinib, respectively. In facts, while in the case of cabozantinib the dose reduction does not impact on pharmacy costs (flat price, that means the same price for the

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Table 1. Pharmacological costs and difference in OS with regorafenib and cabozantinib in advanced HCC after sorafenib.

Authors/Trial	Comparative Regimens	Total N patients	Primary endpoint	OS (months)	p-value	OS gain (months)	OS HR (95% C.I.)	ESMO-MCBS	Median duration of treatment (months)	Costs of therapy (€)	Difference in costs (€)	ICER (€)
Bruix et al. [3] RESORCE	regorafenib	374	OS	10.6	**< 0.001**	2.8	0.63 (0.50-0.79)	3	3.6	7760	7760	2771[a] 2078[b] 1385[c]
	placebo	193		7.8					1.9	0		
Abou-Alfa et al. [1] CELESTIAL	cabozantinib	470	OS	10.2	**0.005**	2.2	0.76 (0.63-0.92)	2	3.8	11 680	11 680	5309
	placebo	237		8.0					2.0	0		

Legend: N: Number; OS: Overall Survival; ESMO-MCBS: European Society for Medical Oncology-Magnitude of Clinical Benefit Scale (from grade 1 to grade 5); ICER: Incremental Cost-Effectiveness Ratio (expressed as the difference (€) per month-OS gained); [a]: at the dose of 160 mg/daily for the first 3 weeks of each 4-week cycle; [b]: with dose reduction at 120 mg/daily for the first 3 weeks of each 4-week cycle; [c]: with dose reduction at 80 mg/daily for the first 3 weeks of each 4-week cycle.

Table 2. A comparison between regorafenib and cabozantinib in advanced HCC with the costs of immune check point inhibitors (ICIs, nivolumab, pembrolizumab and atezolizumab) in the treatment of advanced NSCLC and the costs of the reference elements in international markets (gold, platinum).

Element/drug	Cost per gram (€)	Δ toward gold 18K per gram (€)	Δ toward platinum 18K per gram (€)
gold 18K	46.90	--	--
platinum	21.45	--	--
regorafenib	577.25	530.35	555.80
cabozantinib	1733.33[a] 2600.00[b] 5200.00[c]	1686.43[a] 2553.10[b] 5153.10[c]	1711.88[a] 2578.55[b] 5178.55[c]
nivolumab	107 500.00	107 453.10	107 478.55
pembrolizumab	205 608.00	205 561.10	205 586.55
atezolizumab	1726.03	1680.87	1697.50

Legend: k: Karat; nivolumab: 1070.00 € for 100 mg, pembrolizumab: 2056.08 € for 100 mg, atezolizumab= 2071.24 € for 1200 mg.

different dosages), in the case of regorafenib it implies for a reduction on pharmacy costs of 25% and 50% if we consider the dose reduction at 120 mg/daily and 80 mg/daily, respectively (Table 1).

In addition, we have to consider that the scenario in the advanced HCC is changing, with the recently introduction in first-line of Lenvatinib [8] and the combination of atezolizumab and bevacizumab [9]. So, regorafenib and cabozantinib will be placed in third line (about 30% of patients treated with cabozantinib in pivotal phase III RCT where already in third line [1]. Ramucirumab was not considered in our analysis because it was approved by Food and Drug Administration (FDA) in 2019, but not by European Medical Agency (EMA) [10].

We have also compare the pharmacy cost of regorafenib and cabozantinib with the pharmacy costs of immune check point inhibitors (ICIs), (nivolumab, pembrolizumab and atezolizumab) registered in other tumors (eg. non-small cell lung cancer (NSCLC), head and neck carcinoma, urological malignancies) and known as the most expensive new drugs in medical oncology[11-16], with the costs of the reference elements in international markets, gold 18 karat (K) and platinum. Both regorafenib and cabozantinib have a high cost per gram (even if significantly lower than most ICIs), with 577.25 € (regorafenib), 1733.33 € (cabozantinib, 60 mg tablets), 2600.00 € (cabozantinib, 40 mg tablets) and 5200.00 € (cabozantinib, 20 mg tablets), with a Δ toward gold 18K and platinum per gram of 530.35 € and 555.80 € for regorafenib, respectively and of 1686.43 € (600 mg tablets), 2553.10 € (40 mg tablets) and 5153.10 € (20 mg tablets) and 1711.88 € (60 mg tablets), 2578.55 € (40 mg tablets) and 5178.55 € (20 mg tablets) for cabozantinib, respectively. So, a reduction in pharmacological costs is mandatory if we want to consider targeted agents more advantageous in terms of cost-effectiveness.

In conclusion, based on ICER, regorafenib is a cost-effective for the treatment of advanced HCC after sorafenib. The price of newly registered oncologic drugs is continuously increasing posing a serious treat to the sustainability of the National Health Systems, especially in Countries in which the public control and oversight over the prices is limited. Medical Oncologists and the society as a whole are becoming more and more concerned with the issues of the costs of the cure of cancer patients and are able to bring attention to the "just price" of new treatments that must reflect the reality of their true benefits and societal and personal costs.

Conflict of Interest statement

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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