Editorial Commentary

Design your strategy, define your costs: third or subsequent-lines in advanced gastrointestinal stromal tumors (GIST)

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The topic of costs has become one of the main topics in oncology, as well as in relation to the introduction on target biological agents, with their greatest budgetary impact (1). The treatment of advanced/metastatic gastrointestinal stromal tumors (GIST) has radically changed with the introduction of imatinib (2) in first-line treatment in 2002 (3). In case of progression of the disease (after dose increase of imatinib from 400 to 800 mg/daily), other tyrosine kinase inhibitors (TKIs) are indicated in subsequent lines, with the introduction of sunitinib first in 2006 (4) and regorafenib after in 2013 (5). These indications (sunitinib and regorafenib after imatinib) raises the main problem of pharmacy costs increase. The aim of this paper was to assess the cost-effectiveness of sunitinib and regorafenib in advanced GIST patients in subsequent lines after progression from imatinib.

Pivotal phase III randomized controlled trials (RCTs) were considered (4,5). 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 [progression-free survival (PFS)]. The costs of drugs are at the Mater Salutis Hospital of Legnago (VR, Italy) and are expressed in euros (€) (prices sourced as of December 2020). We assumed the following costs: sunitinib =163.59 € for 50 mg tablet (one tablet per day for 28 consecutive days every 42 days), regorafenib =21.89 € for 40 mg tablet (4 tablets per day for 21 consecutive days every 28 days). The costs used are already consider the confidential rebates.

Five hundred eleven patients were included (4,5). European Society for Medical Oncology-Magnitude of Clinical Benefit Scale (ESMO-MCBS) reached grade 4 for both RCTs. Sunitinib resulted with a cost of 954.28 € per month of PFS-gain and regorafenib with a cost of 2,828.86 € per month of PFS-gain (*Table 1*).

The efficacy of treatment in the first strong variable that could be condition pharmacological costs and efficacy is determined by RCTs results (that are related to the patient's inclusion criteria). This is also the main limit: results from RTCs could be not representative of daily clinical practice (6). The price of drugs is the second strong variable and it is related to the difference in pharmacy costs within different European countries (in Italy there are no significant pharmacy cost differences between the different regional realities), due to the use of local pharmacy cost (referring to external reference pricing). In this specific case, the costs standardization bias is minimized by the comparison with placebo. Another limit is related to the consideration of only the costs of drugs (which account for about 55% of total medical expenses). The cross-trial comparison is an additional limit.

In Europe expenditure for cancer drugs amounted to €10 billion in the year 2005 and increased more than three times to €32 billion in the year 2018 (7). This situation could introduce a new type of resistance, not linked to biological mechanism, but to the increase of costs of novel treatments, that we can call "costs resistance". In several Countries this

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Table 1 Pharmacological costs and difference in PFS with sunitinib and regorafenib in advanced GIST patients in subsequent-lines after progression to imatinib

Authors/trial	Comparative regimens	Total N patients	Primary endpoint	PFS (months)	P value	PFS gain (months)	PFS HR (95% CI)	ESMO-MCBS	Median duration of treatment (months)	Costs of therapy (€)	Difference in costs (€)	ICER (€)
Demetri *et al.* (4)	Sunitinib	207	PFS	6.3	<0.001	4.8	0.33 (0.23–0.47)	3	1.8	4,580.52	4,580.52	954.28
	Placebo	105		1.5					1.0	0		
Demetri *et al.* (5)	Regorafenib	133	PFS	4.8	<0.001	3.9	0.27 (0.19–0.39)	3	5.3	11,032.56	11,032.56	2,828.86
	Placebo	66		0.9					1.6	0		

N, number; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; GIST, gastrointestinal stromal tumors; 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-PFS gained].

could results in precluding new oncological treatments.

To our knowledge, this is the first time an analysis of the pharmacological costs of sunitinib and regorafenib in advanced GIST patients in subsequent-lines after progression to imatinib is linked to PFS.

In addition, the annual perspective to get 12 months of PFS with both sunitinib (11,451.36 €) and regorafenib (33,939.12 €) in this setting are in line with those reported in literature (57,138 €) (8). To this we must add that the margin to define an effective treatment (45,686.64 € for sunitinib and 23,198.88 € for regorafenib) is quite high and difficult to overcame even in presence of significative differences in pharmacy costs between the different countries.

In conclusion, combining pharmacological costs of drugs with the measure of efficacy represented by PFS, both sunitinib and regorafenib could be considered cost-effective treatments in advanced GIST patients in subsequent lines after progression to imatinib.

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