Pharmacoeconomic analysis for K-Ras status based decisions for first line therapy of metastatic colorectal cancer (mCRC)

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ABSTRACT

Background:
Personalized medicine is a challenge for current oncology practice. Nowadays there are no pharmacoeconomic analyses in Spain dealing with the health-economy impact secondary to K-Ras based decisions for first line of therapy in mCRC patients. So, this study was aimed to assess the cost-effectiveness of K-Ras status based decisions in the first- line therapy of mCRC patients in comparison with non- K-Ras based selection of available therapies.

Methods:
K-Ras mutation prevalence and efficacy of available therapies (measured as response rate and progression free survival) were extracted from randomized clinical trials (RCT) that allowed on-label use of accessible drugs in Spain. Then, we have simulated all possibilities of combination therapies for first line mCRC based on K-Ras status (wild- type vs mutated) and confronted with all therapies that could be chosen in absence of K-Ras analysis. Prices for all drugs in Spain were used to assume the best- value for each drug including all possibilities to reduce pharmacy costs. For first line, median duration of therapy reported by RCT was used to calculate the final budget. 70 kg and 1.7 m were used as reference for patients dose calculations.

Results:
First line therapy that includes a biological drug in absence of K-Ras status based decisions implies an incremental cost per 1% of increased response rate of 1237 euros for irinotecan based doublets and 3193 euros for oxaliplatin based doublets. On the opposite, K-Ras based decisions reduces costs per objective response by 69% and 34% for irinotecan and oxaliplatin-based schedules in K-Ras native population incorporating cetuximab as biological agent. These data mimic all calculi based on incremental costs secondary to improved progression free survival measured as HR when all scenarios without prior determination of K-Ras status were confronted with K-Ras based decisions.

Conclusions:
K-Ras based decisions reduces costs per objective response as well as per improved progression free survival. Most cost- effective scenario between all simulated was cetuximab in combination with chemotherapy for patients that harbor wt K-Ras mCRC.

CONTACT DATA

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INTRODUCTION

Current practice of clinical oncology is a challenge where increased efficacy of new-targeted therapies is counteracted by increasing costs. Furthermore, international financial crisis forces national health systems to optimize all therapeutic strategies maintaining clinical outcomes. Personalized medicine tries to select specific subpopulation of patients by biomarkers to refine therapeutic algorithms. However, there are very few studies that evaluate financial impact of biomarkers incorporation to decide therapeutic approaches for cancer patients. In this regard, the population of mCRC patients is an excellent group to test direct costs associated to personalized medicine because of the existence of a single biomarker. K-Ras mutation is associated with absence of benefit for cetuximab-based therapies so it is recommended to assay the mutational status of this oncogene for every candidate that may receive this drug. In consequence, those patients with mutated K-Ras tumors and those without any information regarding K-Ras status, therapeutic possibilities are restricted to chemotherapy alone or bevacizumab- based combinations. We aimed to evaluate financial and clinical impact that K-Ras based decisions on therapies may exert on a population of chemotherapy naïve mCRC patients comparing these results with financial and clinical outcomes for therapeutic choices in absence of K-Ras testing.

METHODS

This study compares direct costs secondary to all possible K-Ras status therapeutic-based decisions to every approach that could be drawn in absence of K-Ras information for patients diagnosed with first-line metastatic colorectal carcinoma (Figure 1). Additionally, direct costs were weighted to objective response rate (ORR) and progression free survival (PFS) to provide cost- effectiveness information that may help physicians to manage all proposed scenarios.

Efficacy data.
Efficacy data for all schedules without a monoclonal antibody were extracted from control arms of RCT that compared bevacizumab or cetuximab- based chemotherapy. Response rate and hazard ratio for progression free survival were considered the most relevant efficacy. Accordingly, HR=1 for PFS secondary to 5FU-leucovorin treatment was used as a reference to weight all HR from doublets and triplets of therapy. All efficacy data according to every RCT are summarized in table 1.

Costs.
We included direct drugs costs and, when needed, K-Ras determination costs. Indirect and medical costs were not included and will be the issue for future studies. Median duration of therapy, dosing and administration schedules were estimated from RCT selected to identify efficacy data for this study. Dosing for a standard patient was calculated considering a weight of 70 kg and a body surface of 1.7 m2. For all drug unit costs, price per mg was calculated using pharmacy retail prices in Spain as of July 2011, the best- value package size, generic drug costs for those available and no wastage for any drug. K-Ras determination costs were included only for K-Ras based decisions. This cost varies according with the technology used to sequence codons of interest (12 and 13 for this study), ranging from 120 euros per patient (RT-PCR assays) to 50 euros per patient when direct sequencing is performed.

Sensitivity analysis.
We changed assumptions for weight, body surface, K-Ras determination costs depending on the technology assayed, K-Ras mutation prevalence and chemotherapy schedules combined with monoclonal antibodies to test whether the results of our analysis were robust.

RESULTS

Base case analysis.
For first line mCRC without mutations in K-Ras, oncologists may choose three alternatives of therapy (cetuximab plus chemotherapy, bevacizumab plus chemotherapy and chemotherapy alone). Additionally, chemotherapy schedules can be oxaliplatin or irinotecan based. In this regard, the model predicted that cetuximab in combination with chemotherapy is associated with an overall response rate (partial response plus complete response) ranging from 59.3% (in combination with FOLFIRI) to 60.7% (in combination with FOLFOX4). Bevacizumab in combination with chemotherapy or chemotherapy alone efficacy are not affected by K-Ras status so their efficacy in terms of ORR is the same in all scenarios. So the model predicted that bevacizumab-based therapies yielded an ORR ranging from 44.8% in combination with IFL to 46.5% when combined with FOLFOX4. Finally, chemotherapy alone is associated with objectives responses of 38.7% and 35.7% using FOLFIRI and FOLFOX4 respectively. Regarding PFS, HR for cetuximab ranged from 0.567 to 0.696 when combined with oxaliplatin or irinotecan- based doublets respectively. Bevacizumab HR for PFS varied from 0.54 to 0.83 when was used in combination with IFL or FOLFOX4 respectively. Similarly, oxaliplatin and irinotecan doublets provided significant HR results when compared with 5FU-LV. However, the entire scenario resulted from the combination of both K-Ras native and mutated decisions. So, we weighted direct costs from specific strategies according to prevalence of K-Ras mutations in a single population. In this regard, combinatorial possibilities were summarized in table 2.

Sensitivity analyses.
Expected differences among scenarios were not affected by variation in weight, body surface and K-Ras determination costs (supplementary data). K-Ras mutation prevalence modified results for direct costs because any increase in wt-K-Ras population above 60% yielded a raise in the final budget as well as any decrease in this value reduced direct costs.

		ORR			HR PFS		
RCT	Schedule	General population	Wt K-Ras	Mut K-Ras	General population	Wt K-Ras	Mut K-Ras
EMR 62 202-013	Cetuximab + FOLFIRI	46.9%	59.3%	-	-	0.696	-
	FOLFIRI	38.7%	43.2%	36.8%			
EMR 62 202-047	Cetuximab + FOLFOX4	45.6%	60.7%	-	-	0.567	-
	FOLFOX4	35.7%	37%	34.8%			
AVG2107g	Bevacizumab + IFL	44.8%			0.54	-	-
	IFL	34.8%					
N016966	Bevacizumab + FOLFOX4	46.5%			0.83	-	-
	FOLFOX4	49%					

Table 1. RCT incorporated to this study.

Therapy	HR PFS	ORR	Patient cost (July 2011 €)
5FU/LV	1	Control	
FOLFIRI	0.66	34%	€ 4,129.85
Bevacizumab + IFL	0.35	65%	€ 29,039.00
Bevacizumab + FOLFIRI	Not reported	p > 0.05	N.A.
Cetuximab + FOLFIRI	0.45	55%	€ 24,354.98
FOLFOX4	0.76	47%	€ 3,320.37
XELOX	0.79	47%	€ 4,533.20
XELOX + Bevacizumab	0.61	p > 0.05	€ 26,847.79
Bevacizumab + FOLFOX4	0.63	p > 0.05	€ 26,419.01
Cetuximab + FOLFOX4	0.43	57%	€ 23,545.49

Table 2. Schedules, efficacy data and direct costs per patient.

	Therapy	Clinical outcomes		Financial outcomes	
Strategy	Wt K-Ras	Mut K-Ras	HR PFS	ORR	Cost per patient
I	Cetuximab + FOLFIRI	Bevacizumab + IFL	0.404	52.6%	€ 26,643.68
II	Cetuximab + FOLFOX4	Bevacizumab + FOLFOX4	0.521	54.1%	€ 24,995.93
III	Cetuximab + FOLFIRI	FOLFIRI	0.544	49.8%	€ 15,110.75
IV	Cetuximab + FOLFOX4	FOLFOX4	0.580	49.1%	€ 14,301.26
V	Bevacizumab + IFL	IFL	0.506	41.8%	€ 16,584.43
VI	Bevacizumab + IFL	Bevacizumab + IFL	0.350	44.8%	€ 29,039
VII	Bevacizumab + FOLFOX4	Bevacizumab + FOLFOX4	0.630	46.5%	€ 26,419.01
VIII	Bevacizumab + FOLFOX4	FOLFOX4	0.692	41.1%	€ 14,869.69

Tabla 3. Combined scenarios (Mut K-Ras plus WT K-Ras)

DISCUSSION

Our results suggest that K-Ras based decisions reduce direct costs in the first line setting of mCRC, maintaining clinical efficacy of few therapeutic approaches. So, this is the first study evidencing that personalized medicine for the management of CRC may save funds and suggests that it should be implemented in clinical practice for the Spanish healthcare system. Although dealing with the most effective schedule for mCRC is not an aim for our study, our data evidence that there are specific algorithms that may optimize both clinical and economic outcomes.
The most expensive approach is to treat all patients with monoclonal antibodies-based therapies. Another result is that maintenance therapies with monoclonal antibodies yield the highest incremental cost whereas absence of maintenance therapy with bevacizumab may lead to reduced clinical outcomes.
Our study also provided significant information for those devoted to get cheaper therapies. In this regard, chemotherapy without any monoclonal antibody provides the cheapest therapeutic approach for this group of patients but reduces clinical efficacy by 20% in terms of radiological responses and increases by 25% the probability of progression along the treatment. Additionally, if we decide to include the cheapest approach that includes a monoclonal antibody in our tactic, we will observe that strategy do not get statistical significance on clinical trials (FOLFOX-bevacizumab) and should be avoided from pharmacoeconomic calculi as well as from clinical practice. We have included this possibility to highlight that cheaper strategies may result in clinical pitfalls.

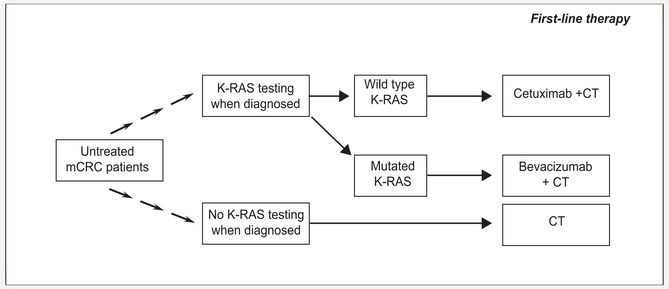

Figure 1. Strategies to compare based on K-Ras mutational analysis.

CONCLUSION

K-Ras based decisions reduce costs per objective response as well as per improved progression free survival. Most cost-effective scenario between all simulated was cetuximab in combination with chemotherapy for patients that harbor wt K-Ras mCRC. Clinical outcomes of bevacizumab combined with chemotherapy rely heavily on administration of maintenance therapy. Absence of a biomarker for this therapy scenarios implies their cost-effectiveness ratios are widely above the usual thresholds.
So, integration of K-Ras mutational status as a keystone to make clinical decisions for mCRC patients is cost-effective and optimizes financial resources for the Spanish National Healthcare System.