Fabiano, Gianluca, Mennini, Francesco, Marcellusi, Andrea, Rimassa, Lorenza, Santoro, Armando and Personeni, Nicola (2019) Budget impact of bi-monthly use of Cetuximab in patients diagnosed with mCRC. Future Oncology, 15(8), pp. 2107-2122. ISSN (print) 1479-6694

https://doi.org/10.2217/fon-2018-0904

Abstract:

Background: Cetuximab is used for the treatment of RAS wild-type metastatic colorectal cancer patients. Standard administration schedule is once a week however the bioequivalence of an every-other-week (EOW) schedule was demonstrated.
Methods: We compared a base case scenario of 100% weekly administration to an every-other-week (EOW) at 50% or 100%. Medical examinations, patient management and loss of productivity were considered.
Results: Base case was estimated at €100.6 million versus € 92.8 million and €84.9 million of EOW 50% and 100% which showed a cost reduction of 8% and 16% respectively. Indirect costs accounted for 65% in both scenarios.
Conclusions: The adoption of an EOW administration schedule of Cetuximab reduced direct and indirect costs substantially.

Introduction

Colorectal cancer (CRC) is a major public health issue of industrialized countries. The management of the high number of patients with metastases heavily impact on oncology services and health resources [1-3]. Moreover, a great increase in social and economic burden is anticipated by changing demographics and the ageing of the population worldwide.

CRC is a highly lethal cancer, depending on its focalization, after 3-5 years of diagnosis the death rate reaches 40-60% [4]. In Italy, according to the Italian Association of Cancer Registries (AIRTUM) and the Italian Association of Medical Oncology (AIOM), there are over 464,000 patients with a previous diagnosis of colorectal carcinoma (53% males), the second most common cancer affecting 14% of all cancer patients [5]. With regard to the incidence, 53,000 new diagnoses of colorectal cancer are estimated in 2017. Furthermore, CRC represents the second most frequently diagnosed cancer among men (13%) and women (16%), preceded by prostate and breast cancers respectively [5].

In the metastatic setting, current treatment options for *RAS* wild-type patients include the administration of chemotherapy in combination with an anti- epidermal growth factor receptor (EGFR) antibody. Indeed, these recommendations are based on significant improvements in terms of overall survival provided by the addition of anti-EGFR antibodies,

namely cetuximab and panitumumab, to standard chemotherapy regimens, such as Folfox or Folfiri [5, 6]. In particular, cetuximab is a chimeric monoclonal immunoglobulin G_1 (IgG_1) administered following a weekly treatment schedule of 400 mg per BSA as loading dose for the first week, and 250 mg per body surface area (BSA) in the following weeks [7]. Due to the long Cetuximab half-life of 66-98 hours, its administration every other week (EOW) is theoretically possible although the weekly schedule was validated in clinical studies. Pharmacodynamics (PD) and pharmacokinetic (PK) studies demonstrated the bioequivalence as well as the efficacy of an EOW dosing schedule [6, 8-10] in mCRC *RAS* wt patients [11], however the economic consequences have yet to be thoroughly investigated. The objective of the analysis was to assess the impact on National Health Service budget of a bi-montly administration method (EOW) of Cetuximab in patients diagnosed with mCRC RAS wt in Italy.

Methods

An excel-based model was developed to estimate the economic impact of an (every other week) EOW compared to weekly administration of Cetuximab among patients with mCRC RAS wt. We performed a review of the epidemiological and economic literature. The budget impact model was developed following the guidelines suggested by the International Society of Pharmacoeconomics and Outcome Research (ISPOR) [12, 13].

Epidemiological parameters

The size of the eligible population in Italy was identified according to therapeutic indication of Cetuximab. As reported in Table 1, incidence rates provided by the Italian Association of Cancer Registries [5] were used to estimate the cohort of individuals annually diagnosed with CRC on the total resident population at 2017 [14]. Then, the number of patients diagnosed with mCRC *RAS* wt was estimated considering the average between those that presented metastasis at initial diagnosis and those that were likely to develop metastases after [15]. Precisely, the model assumed that about 21,730 patients had a metastatic CRC

and 5,067, corresponding to 23.3%, were *RAS* wild type [16, 17]. Of these, 2,787 patients (55%) were treated with first line Cetuximab [18].

Table 1 – Epidemiological parameters to identify the population diagnosed with CRC-RASwt – Italy 2017

Epidemiologic Parameters mCRC	Model Parameter	Population	Ref
Residential population		60,589,445	[14]
CRC incidence	0.087%	53,000	[5]
mCRC wt population	41.0%	21,730	[15]
Popolazione mCRC wt - EGFR+	23.3%	5,067	[16, 17]
Patients treated with Cetuximab	55.0%	2,787	[18]

Time Horizon

The second step included the definition of the time horizon. With reference to mCRC *RAS* wt patients, a 6-months time horizon has been considered. Irrespective of primary tumor location [19], this figure reflects the overall duration of cetuximab as part of the first-line treatment, either in association with chemotherapy or after withdrawal of chemotherapy (maintenance) [20]

Current and future treatment mix

In keeping with the current administration schedule, a base case scenario was set considering 100% of patients treated with a weekly administration of Cetuximab with a first loading dose as per the technical sheet [7]. In the comparison scenario the base case administration was replaced with every-other-week (EOW) administration at 50% or 100% of the eligible population for the maintenance therapy only. In the base case scenario the schedule included a dose of 250 mg per BSA [7] compared to one dose of 500 mg per BSA every two weeks (alternative scenario). Moreover, the expense simulations have been broken down in cost analyses per mg of drug used (base case) and per required ampoule (included in sensitivity analysis). The model assumed an average BSA of 1.8 m^2 [21], details on the treatment schedules are reported in Table 2.

Cost Parameters

According to the dosing schedules (Table 2), the price of Cetuximab was used net of discounts by law. Furthermore, the costs associated with patients' management have been included. Precisely, we estimated the cost of medical examinations required for drug administration and patient management. We considered a cost of €85 per medical examination for each administration. This includes the cost of the physician, nurse, consumption material, for the drug administration and distribution by the hospital pharmacy [22]. Moreover, indirect costs associated with the loss of productivity (absence from work) of the patient or caregivers were estimated. The model assumed the loss of one working day every time the drug was administered to the patient in the hospital setting. We calculate these by considering an average salary per hour of €27.8 [23, 24], which corresponds to a daily salary of €200.2 [23, 24] before tax, (Table 2).

Finally, the model did not consider efficacy and safety differences between the two schedules and chemotherapy costs were not included as they were the same for the two strategies.

Table 2 – Parameters of patient definition and therapy cost

Parameters of patient definition mCRC RAwt	Parameter	Ref
BSA patient, m^2	1.8	[21]
Weekly ampoule weekly I CET / 400mg per BSA	8.0 / 720mg	[7]
Weekly ampoule II CET_Weekly/ 250mg per BSA	5.0 / 450mg	[7]
Weekly ampoule CET_EOW/500 mg per BSA	9.0 / 900mg	Assumption
Number of lost working days per medical examination	1.0	Assumption
Cost parameters	**Cost**	**Ref**
Ampoule price 100 mg	€ 153.6	AIFA
Cost of medical examination per administration	€ 85.0	[22]
Cost of working day Italy	€ 200.2	[23, 24]

Sensitivity Analysis

In order to account for the model uncertainty due to parameters and the consequent variability on results, a deterministic one-way sensitivity analysis was performed. This was performed by varying one parameter of the model at once, depending on the variability observed in the literature or assumed by the authors as advised by clinical experts. The

consequence of such variations were observed on BI results. Specifically, the following scenarios have been considered and applied on the 100% EOW scenario compared to base case:

- ✓ mCRC RAS wt patients treated with Cetuximab (base-case=55.0%): Min=45% - Max 65%
- ✓ Cost of drug by number of ampoules required for the administration (base case=cost per mg)
- ✓ Working days lost per visit (base case=1 day lost): Min = 0 – Max = 2
- ✓ Incidence of CRC (base case=0.087): Min=0.078% - Max: 0.096%,

Results

We estimated a total of 2,549 patients diagnosed with mCRC RAS wt. In the base case scenario these were subjected to first-line treatment with Cetuximab once a week and compared with an EOW administration schedule applied to 50% and 100% of patients. In the next sections the results of these comparisons are illustrated.

Base case vs EOW 50% Scenario

When 50% of patients were subjected to bi-monthly administration with Cetuximab, the budget was expected to decrease from €100.6 million in the base case to €92.8 million in the scenario, resulting in an overall net savings of 8% or €7.8 million. The greatest savings came from indirect costs that were reduced by €5.1 million corresponding to 25% followed by those related to the management of patients and drug administration (-24% with respect to base case). Drug costs showed a smaller saving of approximately €528.4 thousand (-0.7%).

Table 3 – Budget Impact results base case vs EOW 50% Scenario

ITALY 10-month results	Expense		
	Base case	EOW 50% Scenario	BUDGET IMPACT
Drug cost (calculation per mg)	€ 43.328.094	€ 42.799.703	**-€ 528.391**
Management cost/ drug administration	€ 5.199.649	€ 3.899.737	**-€ 1.299.912**
Indirect costs	€ 12.246.703	€ 9.185.027	**-€ 3.061.676**
TOTAL EXPENSE	**€ 60.774.446**	**€ 55.884.467**	**-€ 4.889.979**
	1 Week	EOW 50% Scenario	Tot treated patients
Treated patients base case	2,549	0	2,549
Treated patients 50% Scenario	1,274	1,274	2,549

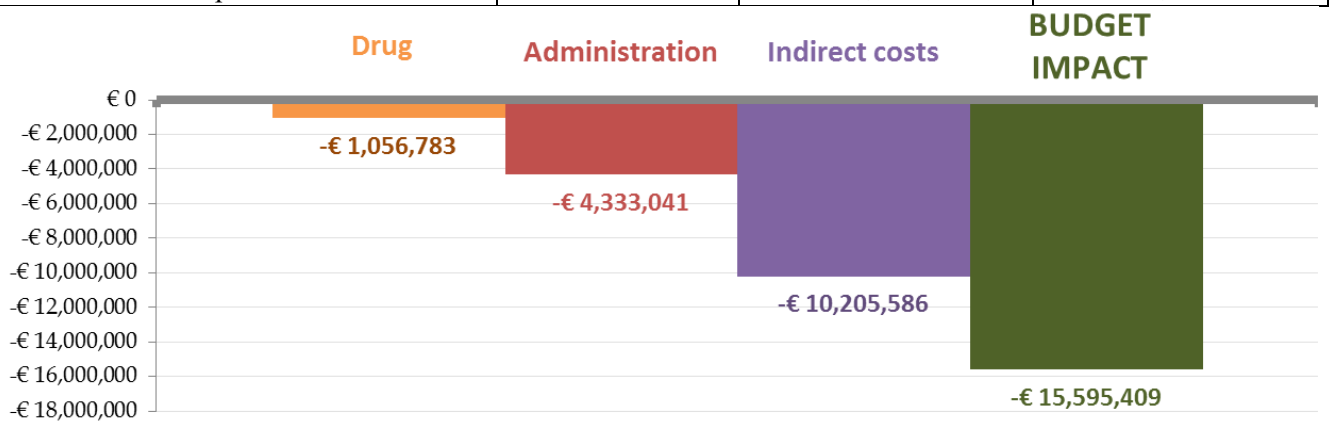
Base case vs EOW 100% Scenario

An EOW administration of Cetuximab on 100% of the eligible population resulted in a greater reduction on the 10-months budget. Precisely, the budget was reduced to €84.9 million compared to the base case scenario (€100.6 million), resulting in an overall cost savings of 16% or €15.6 million. As reported in Table 4, the greatest savings were due to

indirect costs (over 50% reduction), from €20.4 million in the base case to €10.2 in the scenario. Management costs, including cost of medical examinations and drug administration, decreased by €4.3 million, resulting in a reduction by roughly 50% compared to the base case (€8.6 million). Drug costs were the smallest category driver of cost reduction with a savings of €1.05 million.

Table 4 – Budget Impact results base case vs EOW 100% Scenario

ITALY 10-month results	Expense		
	Base case	EOW 100% Scenario	BUDGET IMPACT
Drug cost (calculation per mg)	€ 71,508,968	€ 70,452,186	**-€ 1,056,783**
Management cost/drug administration	€ 8,666,082	€ 4,333,041	**-€ 4,333,041**
Indirect costs	€ 20,411,171	€ 10,205,586	**-€ 10,205,586**
TOTAL EXPENSE	**€ 100,586,221**	**€ 84,990,812**	**-€ 15,595,409**
	1 Week	EOW 100% Scenario	Tot treated patients
Treated patients base case	2,549	0	2,549
100% treated patients Scenario	0	2,549	2,549

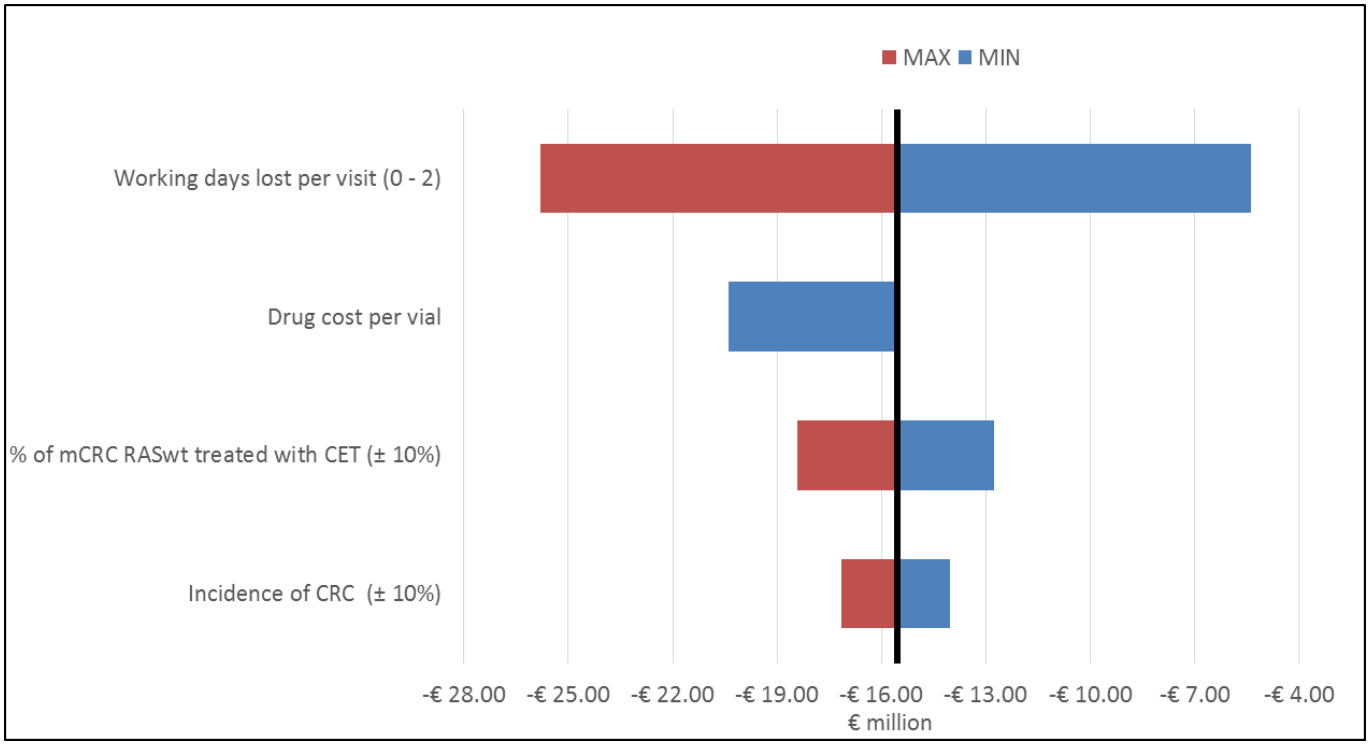


Sensitivity Analysis

Figure 1 shows the variables with the highest impact on the model results. The model was most sensitive to the number of working days lost by patient or caregivers that accounted for approximately 41% of variation in model outputs, with budget impact results ranging from -€5.4 million to -€25.8 million in the 100% EOW scenario compared to base case. The adoption of cost per ampoule would cause incremental savings of €4.8 million compared to the base case, resulting as the second most influential category over model variability. The variation of +/-10% hypothesized over the incidence of mCRC RAS wt

patients and the number of those treated with Cetuximab resulted in a relative small impact on the model results accounting for 11% and 9% on the overall variability respectively.

Figure 1 – One-way sensitivity analysis - Case base Budget Impact vs EOW 100% scenario



Discussion

This budget impact analysis was developed to estimate the economic consequences of the adoption of an EOW administration schedule among patients diagnosed with mCRC in Italy. Two different scenarios, when 50% and 100% of patients were treated with the bi-monthly schedule, have been analysed compared to a base case in which the standard of care of a weekly administration was included. The model results showed a net savings ranging from €7.8 million to €15.6 million when adopting the 50% or 100% scenario compared to base case respectively. In both cases, indirect costs were the main driver of cost savings, accounting approximately for the 65% of the overall reduction.

Several factors should be considered when interpreting the results of this analysis. As such, a number of simplifying assumptions were made to develop the model that may impact the study findings. First, the epidemiological parameters, based on published national and international reports may result in an overestimation as well as underestimation of the real number of patients treated with Cetuximab in the Italian context. This aspect was taken into account in the sensitivity analysis where a variation of +/- 10% has been considered accordingly to expert opinions to enable a better estimation of a plausible range. Secondly,

the model may have resulted in an underestimation of direct costs due to the limited number of cost items included in the analysis. In particular, the model considered only the costs of Cetuximab as a drug therapy while the costs of chemotherapy, adverse events and/or disease progression, were not included. This was due to the assumption, validated by clinical experts, that such items would remain unchanged when switching from a weekly to an EOW schedule, thus their inclusion would not affect the study results. a third limitation was represented by the lack of information on the number of working days lost by patients or caregivers that may influence the estimation of indirect costs. Also, presenteeism or absenteeism due to adverse events, the reduced productivity and the risk of dismissal were not taken into account resulting in a further potential underestimation of the budget impact related to indirect costs.

Conclusions

This budget impact analysis demonstrated that the adoption of an EOW administration schedule of Cetuximab among patients diagnosed with mCRC in Italy is expected to reduce direct and indirect costs substantially. Therefore, in addition to the therapeutic equivalence of the two indications of Cetuximab as already demonstrated in previous published articles, the present study provided a measure of the cost savings that would therefore allow a more efficient use of resources at hospital base.

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