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Cost Effectiveness Analysis of Instanyl for the Treatment of Breakthrough Cancer Pain (BtcP)

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Abstract

Background: Breakthrough cancer pain (BTcP) is a transitory exacerbation of the intensity of the pain in a patient with background pain that is well controlled by analgesic treatment (with morphine). The drugs most widely used to treat individual episodes of BTcP are the opioids. Better results can be obtained with Instanyl. So far, while several studies have proven the effectiveness of Istanyl, limited evidence is actually available on the economic affordability for a third party payer (i.e. National Healthcare Systems). In this paper we perform a cost effectiveness analysis, whose aim is to estimate the cost per Quality Adjusted Life Year (QALYs) of Istanyl compared to the use of morphine.

Methods: The analysis was carried out by constructing a Markov model that simulates the natural history of a hypothetical cohort of 100 advanced cancer patients: the patients in the case arm of the study are treated with Instanyl, and those in the control arm with morphine. Consistently with the Instanyl treatment indications, the hypothesis was that patients would have a minimum of 1 to a maximum of 4 episodes of BTcP per day, and that administration of Instanyl might cause side effects which influence both cost and quality of life (QoL). Based on the data in the literature, we populated our model considering the probability of the daily frequency of episodes of BTcP and the associated probability of side effects reported in the literature. Quality of life weights were used to differentiate the health status associated to BTcP depending on whether Instanyl or placebo was used. Probabilistic sensitivity analysis was conducted to assess the variability of results associated to the variation of costs, side effects episodes, daily BTcP episodes and BTcP prevalence.

Results: The results of our analysis show that the treatment of BTcP with Instanyl costs 8,893 euros with an outcome of 0.63 QALYs, whilst the treatment with morphine costs of 6,431 euros for a QALY of 0.29. These data generate an ICER of 10,140 euros/QALY. Overall, the Cost Effectiveness Acceptability Curve shows that the treatment of BTcP with Instanyl would have an 86% probability of having a cost lower of 30,000 euro/QALY. The results clearly show that Istanyl administration is a good and sustainable investment in health, despite the collateral effects and the short life expectancy of advanced cancer patients.

Keywords: Cancer; Instanyl; Opioids

Introduction

Cancer is a disease that is very widespread in every country in the world, especially in industrialized countries. In Italy there are an estimated 300,000 new cases of cancer/year, with an estimated mortality of around 160,000 and a prevalence of around 3% [1,2]. The most common symptom of cancer patients is pain, which is categorized in two forms: background pain (baseline pain or persistent pain) to be treated with fixed doses of analgesic treatment at pre-determined times, and intense episodic or Breakthrough Cancer Pain (BTcP), which needs drug treatment on demand. BTcP is a transitory exacerbation of the intensity of the pain in a patient with background pain that is well controlled by analgesic treatment (with morphine) administered continuously [3]. Background pain, which lasts for 12 hours or more, is distinguished from BTcP, which is characterized by short duration, rapid onset and severe intensity. The duration and intensity of BTcP have been studied by several authors.

According to Zeppetella and Ribeiro [4] the mean duration is 30 minutes, and less than one hour in 90% of episodes [3,5]. Similar results were presented from a study carried out by Gomez-Batiste et al. [6] in which the mean duration was 33.8 minutes with 87% of the episodes of less than 60 minutes' duration, and 31% resolved after 15 minutes (Figure 1). While for intensity, the study carried out by Portenoy et al. [7] reported that maximum intensity was reached within 3 minutes of onset. The pain event may be caused by the primitive neoplastic lesion, bone metastases, chemotherapy, radiotherapy, peripheral nerve or medullary compression, abdominal colic, oral mucous membrane lesions (triggered by swallowing or chewing), skin lesions, or muscle spasm. Pain presents a considerable impact on the quality of life of cancer patients, since it limits the patient's movement and capacity to conduct a normal life (Figure 2), and has effects that are not only physical but also psychological, with a significant increase in levels of depression and anxiety [7] and healthcare system resources. In particular, there is greater recourse to specialist and non-specialist medical consultations, hospitalization and prolonged hospital stays [8]. The study carried out by Fortner et al. [9] reports the cost per patient with BTcP is $ 12,000/year compared to $ 2,400/year for patients who do not present BTcP. The drugs most widely used to treat individual episodes of BTcP are the opioids. The choice of administration route is an important criterion in the decision to treat BTcP, since it influences the time at which the analgesic action appears [4]. The first routes used to administer drugs were oral (e.g. morphine), but this mode of administration proved too slow, and not capable of decreasing the development of intense

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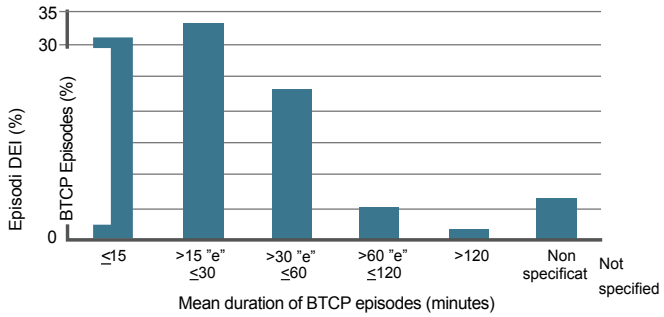

Figure 1: Duration of BTcP episode Source [6].

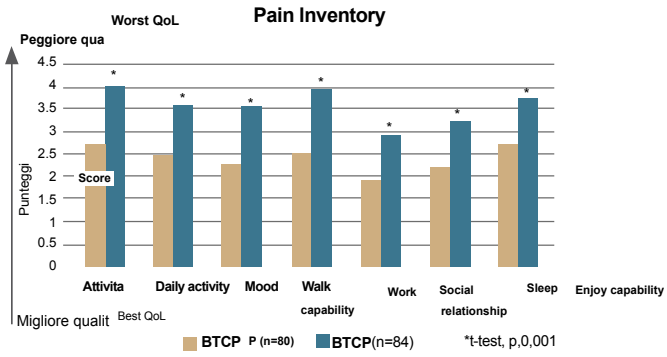

Figure 2: Effect of BTcP on quality of life.

pain in a short period of time. Other administration routes, such as intravenous and subcutaneous have displayed the same limitation as oral administration, apart from transmucosal administration, which permits fast absorption and hence the rapid appearance of analgesic action [10]. To overcome this limitation researchers have focused on new drugs that can act rapidly on the pain. The appearance of fentanyl (e.g. Actiq) on the market was a step forward: this permits faster speed of action than traditional drugs, although it is still too slow to be able to guarantee immediate relief of pain in the patients treated. Better results were obtained with Instanyl. Intranasal administration guarantees greater benefits for the patient compared to other drugs, since it presents a shorter mean duration of action than Actiq: 56 minutes compared to 2 hours, which follows the time trend of BTcP (30 minutes) better. It also permits a lower risk of deglutition, and the consequent passage into the alimentary tract, guaranteeing better capacity of absorption of the active substance. So far, while several studies have proven the effectiveness of Istanyl, limited evidence is actually available on the economic affordability for a third party payer (i.e. National Healthcare Systems). As long as the treatment is available for advanced cancer patients, with a limited life expectancy, one could argue about the "opportunity cost" of allocating resources to these patients instead of others with probably higher chances of living longer. The question is even more challenging when the decision maker is a private insurer. The only way to address this question is to perform a cost effectiveness analysis, whose aim is to estimate the cost per Quality Adjusted Life Year (QALYs) of Istanyl compared to the use of morphine. In this paper we present the results of this analysis.

Methods

Structure of the analysis

The analysis was carried out by constructing a Markov model that simulates the natural history of a hypothetical cohort of 100 advanced cancer patients: the patients in the case arm of the study are treated with Instanyl, and those in the control arm with morphine. Consistently with the Instanyl treatment indications, the hypothesis was that patients would have a minimum of 1 to a maximum of 4 episodes of BTcP per day, and that administration of Instanyl might cause side effects which influence both cost and Quality Of Life (QoL) (Figures 3 and 4). The natural history lasted 7 years, the maximum time in which, all the patients would die [1,2], considering the average mortality of an advanced cancer patient.

The probabilities of having BTcP were taken from the literature as well as the mortality rates for cancer patients. Table 1 shows the prevalence of BTcP in the data reported in the literature from 1990 to 2003 [4], which show great variability (20-93%). This is due to the different patient sampling methods and the absence of tools that can diagnose pain in cancer patients. Considering the mean prevalence reported in the studies below, we estimated a probability for oncologic patients of 56.3% of having BTcP (Figure 3).

Effectiveness data

To include the effectiveness of Instanyl in our model, we selected three clinical studies from the literature. Two of these studies compare Instanyl with placebo, while the third compares Instanyl with Actiq.

Author	Year	Prevalence	Author	Year	Prevalence
Portenoy	1990	65%	Caraceni	1999	65%
Banning	1991	93%	Portenoy	1999	51%
Bruera	1992	20%	Zeppetella	2000	59%
Mercadante	1992	31%	Swarwick	2001	93%
Ashby	1992	35%	Natal	2001	60%
Grond	1996	59%	Fortner	2002	63%
Fine	1998	56%	Gomez-Batiste	2002	41%
Petzke	1999	40%	Hwang	2003	70%

Table 1: Prevalence of BTP: evidence from studies.

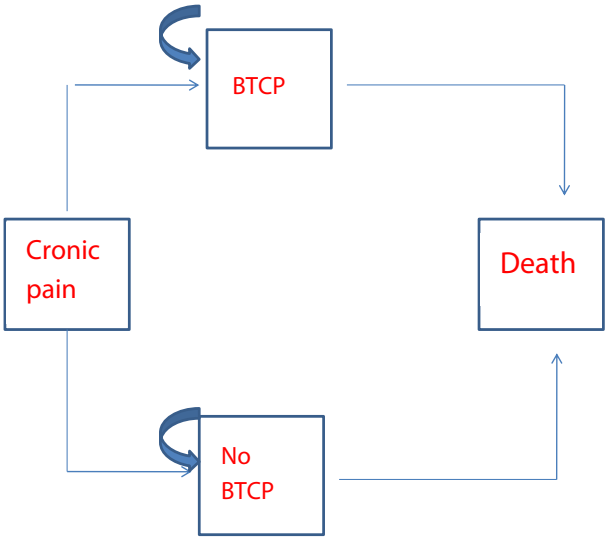

Figure 3: Markov model.

The studies show that Instanyl is more effective, compared to both placebo and Actiq, thanks to the increased speed of its analgesic activity, and hence to its more rapid pain relief (a reduction of 31.25% in the time taken to achieve the analgesic effect) [11-13].

Cost data

Based on the data in the literature, we populated our model considering the probability of the daily frequency of episodes of BTcP and the associated probability of side effects reported in the literature [3]. Regarding the probability of having 1 to 4 episodes per day, we considered the following probabilities:

- 1 or 2 episodes 20%;
- 3 episodes: 50%;
- 4 or more episodes 10%.

Each of these episodes was associated a cost of 5.87 euros when treated with Istanyl and a cost of 2 euros per day when treated with morphine.

Consistently with the administration of Istanyl, we estimated a probability of having side effects (nausea, vomiting, asthaenia, diarrhoea, constipation) of 3% [3-4,13]. These side effects were treated with Plasil © (expert opinion), at a daily cost of 1 euro. Finally, table 1 reports the hospitalizations, days of hospital stay, visits and emergency visits considered by Fortner et al. [9] which were used to estimate the costs to the Italian national health service perspective. Hospitalizations were given a cost of euro 700, by referring to the oncology DRG (Diagnosis Related Groups) tariffs and the mean cost of a day of hospitalization reported by the Italian Ministry of Health [14]. The mean cost of Emergency access [15] was estimated 125 euros, and the cost of a medical consultation as reported by the Italian tariff for outpatient services [16] as 20.66 euros.

Quality of Life (QoL)

Quality of life weights were used to differentiate the health status associated to BTcP depending on whether Instanyl © or placebo was used. Using the data in the literature [3,5,7,11,17] and expert opinion, we associated to patients treated with morphine a QoL value of 0.001 and to patients treated with Istanyl a QoL value of 0.46.

Presentation of results and sensitivity analysis

The results were expressed in the form of Incremental Cost Effectiveness Ratio (ICER): the difference between the costs of Instanyl (considering side effects) and the costs placebo were related to the difference in Quality Adjusted Life Years (QALYs) between Istanyl and morphine. Probabilistic sensitivity analysis was conducted to assess the variability of results associated to the variation of costs, side effects episodes, daily BTcP episodes and BTcP prevalence. This analysis returned a set of different ICERs which were plotted into a cost effectiveness plane and a Cost Effectiveness Acceptability Curve (CEAC) to show the probability of Istanyl to cost less of 30,000 euros/QALY.

Results

Table 2 shows the results of our analysis. The treatment of BTcP with Instanyl costs 8,893 euros with an outcome of 0.63 QALYs, whilst the treatment with morphine costs of 6,431 euros for a QALY of 0.29. These data generate an ICER of 10,140 euros/QALY (Table 3).

Sensitivity analysis

The sensitivity analysis shows as changing the number of side effects, visits, hospitalizations, BTcP prevalence and episodes, the ICER can increase of 30% or decrease of 40% (Figure 5). For example, in the case of 2 BTcP episodes per day, the ICER would be 5,764 euros/QALY, while in the case of 4 episodes per day the ICER would rise to 17,190 euros/QALY. Overall, the Cost Effectiveness Acceptability Curve shows that the treatment of BTcP with Instanyl would have an 86% probability of having a cost lower of 30,000 euro/QALY (Figure 6).

Events	Patients with BTcP (n=160)	Patients without BTcP (n=89)
Mean hospitalizations/year	1	0.4
Mean stay in hospital (days)	7.1	4.1
Mean emergency department visits/year	1.3	0.5
Mean doctor visits/year	4.2	0.6

Table 2: Healthcare resource cost drivers [9].

	Instanyl	Placebo	INCR COST	INCR QALY	ICER
Costs	€ 9,893	€ 6,431	€ 3,461	0.34	€ 10,140
QALY	0.63	0.29			

Table 3: ICER.

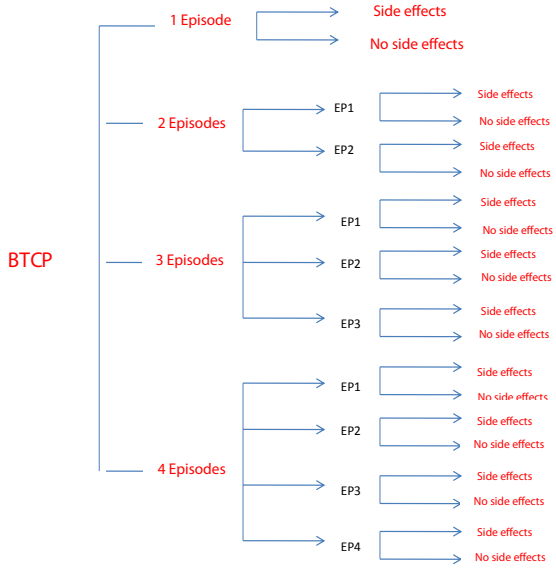

Figure 4: Decision tree to model side effects.

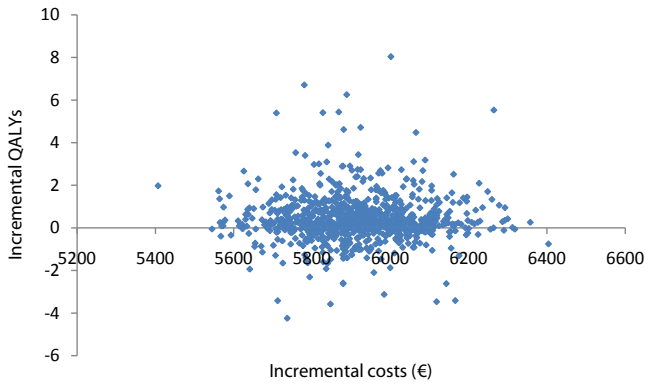

Figure 5: Cost effectiveness plane.

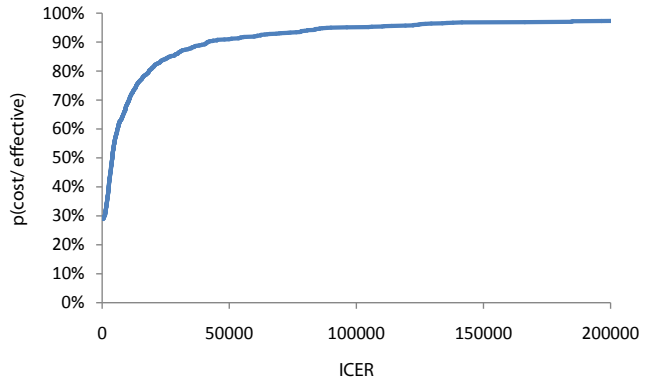

Figure 6: Cost effectiveness acceptability curve (CEAC).

Discussion

In this article we have carried out cost effectiveness analysis of the treatment with Instanyl for Breakthrough Cancer Pain (BTcP), in comparison with the administration of morphine. The results clearly show that Istanyl administration is a good and sustainable investment in health, despite the collateral effects and the short life expectancy of advanced cancer patients. The principal motivation is the gain on quality of life, given the extreme severity of the disease. BTcP is in fact a manifestation of cancer that worsens the patient's perception of the disease, in a clinical situation that is already heavily compromised.

Instanyl, as the principal effectiveness findings show, is an appropriate therapeutic option for the clinical management of BTcP. Intranasal administration is not invasive, results in high bioavailability without the first passage effect, and is well accepted, because it is easy for most patients to manage. In addition, Instanyl can be also used in the same way by patients with xerostomia, nausea and oral mucositis, unlike oral transmucosal formulations.

As a result, Instanyl constitutes an effective treatment innovation, given its documented pharmacokinetic profile and clinical efficacy.

The favorable cost-effectiveness ratio supports the sustainability of Instanyl in economic terms too. The results of the economic assessment are in line with a similar recent study, in Sweden, which reported an ICER of 12,203 euros/QALY. However, it should be noted that this study compared Instanyl with alternative treatments in terms of administration route (transmucal and oral) [18]. The study has strength and weakness which need to be pointed out. Firstly, the work was carried out based on a hypothetical cohort of patients to whom the cost data and evidence of efficacy results of the related trials were applied. While this allows projection of the results in time, and generalisability of the results, it does not represent real data, which would require the design of an ad hoc study to collect real cost data. Secondly, the model considers generic cancer patients, and does not consider the various diseases in the area of oncology. Regarding this, it must be stated that there is as yet no specific information on different efficacy for various diseases, nor is there even the possibility of differentiating. However, the accuracy of the sensitivity analysis carried out lead us to assume that the different scenarios represented different oncologic disease, although they are not specifically identified. A similar consideration may be made regarding the level of severity and the staging of the cancer. Thirdly, the study considers quality of life ratings for an Italian population for the first time and the algorithm for this population is still in the external validation phase, at present. If on the one hand the use of as yet unpublished coefficients may be considered a distortion factor, on the other, they provide more conservative results than the coefficients that are officially used, relating to a British population. In support of this, it is enough to consider that the episodes of BTcP without Instanyl administration correspond to a British population QoL coefficient that is negative (worse than death) while the corresponding value in the case of the weights used in the study at that health status is just above 0. Moreover, the QoL coefficients that summarise the health status are based on the expert opinions and assume changes only in the perceptions of pain (from moderate to severe). In reality, even worse health states could have been hypothesised, given that, again according to the expert opinions, the BTcP patients also experiences a negative impact on mobility, anxiety and daily activities. In this case too, the choice of maintaining a difference between BTcP with and without the administration of Instanyl based solely on pain is prompted by the desire to present conservative results, with a sensitivity analysis that also includes scenarios that are different but increasingly favourable to the treatment considered in this economic assessment.

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