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# Pharmacoeconomic aspects of FOLFIRI or FOLFOX regimens administered with a fully ambulatory pump compared to the day hospital setting

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## ABSTRACT

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**Aims and background.** The social cost of management of patients suffering from colorectal cancer has been growing dramatically in the last decade due to the high number of active antitumor agents and to the increased incidence of the tumor in western countries. The aim of the study was to explore from a pharmacoeconomic point of view a different way to administer the two most common regimens in this patient setting.

**Study design.** This was a cost-minimization study. Data were extracted from hospital registries and dedicated offices. The traditional setting (day hospital inpatient setting) and a fully ambulatory setting (CIP™ pump) were considered and compared.

**Results.** The CIP™ system resulted in higher direct costs than the day hospital setting (444.70 vs 159.00 euro/cycle). However, traditional infusion resulted in longer nursing care, with an increase in nursing costs of more than 100.00 euro/cycle. Moreover, the inpatient setting obliged patients to stay in the hospital as much as ten times longer than with the CIP™ system. This meant that with the same time span and the same resources, the CIP™ pump permitted treatment of at least five times more patients than the traditional setting. Thus, a threshold of 52.00 euro per patient for general hospital costs (ordinary and extraordinary maintenance of buildings, power supply, and housekeeping) was identified to discriminate whether the CIP™ pump is cost-saving or not.

**Conclusions.** Administration of the FOLFIRI or FOLFOX regimen in a traditional day hospital setting was less costly when considering the direct costs. However, a fully ambulatory pump permitted to better employ hospital resources and could permit cost-saving in those units in which more than five patients per day are treated and global costs are higher than 52.00 euro per patient. Free full text available at [www.tumorionline.it](http://www.tumorionline.it)

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## Introduction

The management of patients suffering from colorectal cancer has considerably changed in the last decade. The introduction of irinotecan and oxaliplatin, and more recently of the new biological agents cetuximab and bevacizumab has improved patient outcome in the adjuvant and in the metastatic setting<sup>1</sup>. This increase in treatment efficacy could be the principal mechanism underlying the described decrease in cancer mortality despite the rise in the number of new cases per year<sup>2,3</sup>.

Since the late '60s, the backbone of all chemotherapeutic regimens has been 5-fluorouracil (5-FU)<sup>4</sup>. The pharmacokinetics of 5-FU is well known. Toxicity and efficacy profiles of the compound differ according to whether it is administered with a bolus or an infusional scheme. In particular, infusional administration has been demonstrated to be more active with fewer side effects<sup>5,6</sup>. Today the FOLFOX and FOLFIRI regimens combined or not with biologic agents are the gold standard<sup>4</sup>. These regimens consist

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in the combination of oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) with bolus and infusional 5-FU modulated by folinic acid (Figure 1). They could be administered in a fully inpatient setting or on a day hospital basis with ambulatory pumps. The former solution is being abandoned due to high social and psychological costs, and most patients are treated on a day hospital basis. In this case, oxaliplatin or irinotecan, folinic acid and 5-FU bolus are administered in hospitals in a traditional way with solutions, whereas 5-FU infusion is made possible through ambulatory pumps. Several devices have been proposed to permit 5-FU infusion at home: electronic pumps, more costly and more precise, and elastomeric pumps, less costly but less precise. Factories have now abandoned the development of electronic pumps, focusing their attention on new elastomeric devices that could represent a good compromise between infusion precision and cost savings.

However, it should be noted that the incidence of colorectal tumors is growing with public health costs, which are dramatically increasing. Thus, every new way to administer FOLFOX or FOLFIRI regimens should be carefully considered from a pharmacoeconomic point of view<sup>7</sup>. For an Oncologic Unit which administers more than 1000 FOLFOX or FOLFIRI regimens per year, the choice of a less expensive pump could represent a considerable cost savings. However, a real public health cost savings is represented by a radical change in the management of these patients by reducing their time in the hospital. This might be possible using disposable devices that manage folinic acid and bolus 5-FU and infusional 5-FU administration, and, even better, disposable devices that can administer the complete scheme (oxaliplatin or irinotecan, bolus and infusional 5-FU and folinic acid) in a fully ambulatory setting. In this way, hospital resources would be better employed with a more rational distribution of work, making it possible

to satisfy more patients than would be followed in the same time span.

In this cost minimization study, we considered the pharmacoeconomic aspects of a new device (CIP<sup>TM</sup> pump, H.S. Hospital Service S.p.A., Rome, Italy) that allows administration of FOLFOX and FOLFIRI regimens in a fully ambulatory setting.

**Materials and methods**

We took into consideration two different ways of administering the FOLFOX or FOLFIRI regimen: the traditional setting and the fully ambulatory CIP<sup>TM</sup> pump. These regimens consist of a 1 h 30 min infusion of oxaliplatin or irinotecan on day 1, of a 2-h infusion of folinic acid on days 1 and 2, of a 15 min bolus infusion of 5-FU on days 1 and 2, and of 44 hr continuous 5-FU infusion (Figure 1)<sup>8</sup>. Usually, supportive care such as antiemetics are administered as an infusion in the traditional setting with additional 30-40 min of patient care time, whereas they are administered per os in the CIP setting.

In the traditional setting, drugs are infused in different solutions: 500 cc of 5% glucose for oxaliplatin (or 500 cc of NaCl isotonic solution for irinotecan), 250 cc of 5% glucose for 5-FU bolus, 500 cc of NaCl solution for folinic acid, and an elastomeric pump with no more than 84 cc of 5% glucose solution for 5-FU continuous infusion. CIP pumps consist of 4 elastomeric 160 cc pumps filled with drugs (oxaliplatin or irinotecan, folinic acid and 5-FU) diluted in 5% glucose or NaCl solution as appropriate.

In this cost minimization study aimed to verify which form of administration of the same regimen permits higher cost savings, we did not consider drug, central venous catheter or needles and disinfectant costs in the final computation as they do not differ in the two treat-

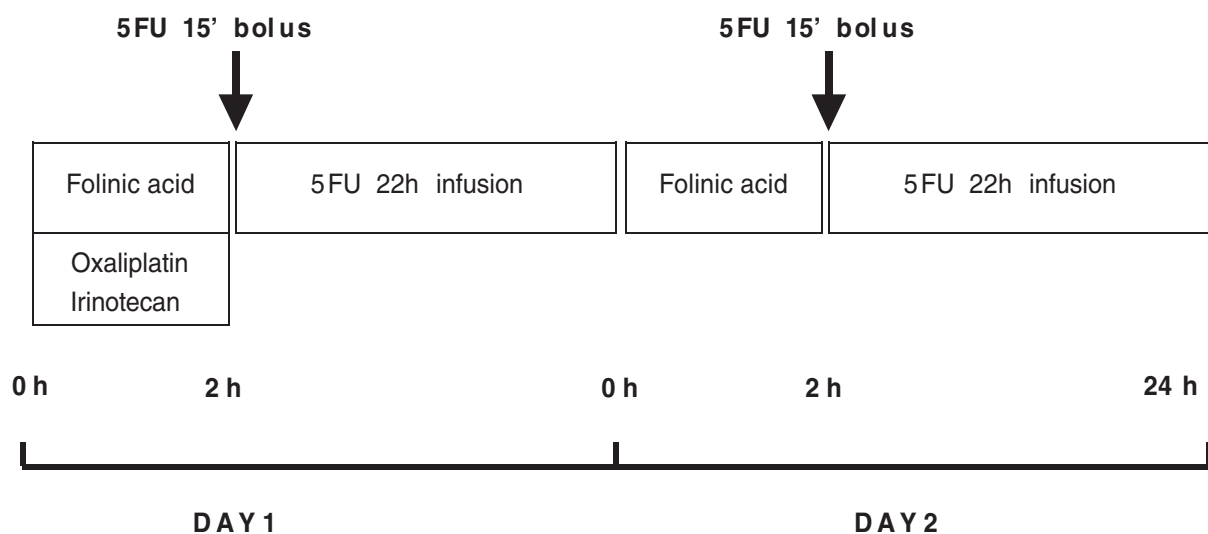


Figure 1 - Infusional scheme of the FOLFOX or FOLFIRI regimens.

ments considered. All costs are expressed in 2008 Euro and VAT is included.

### Hospital costs

Costs of solutions, syringes and infusional pumps were obtained from the Pharmacy registries. Nurse and doctor staff costs as well as meal and inpatient electronic pump costs were provided by the Hospital management control office, particularly dedicated to control money fluxes. Drug, solution, and pump preparation protocols were defined according to the Oncologic Unit of AOU San Luigi Gonzaga, Orbassano, Torino, Italy and compared to major Hospitals in the Piedmont region.

Infusional times are those indicated in the literature, whereas nursing times were measured as follows: for each preparation protocol (drug dilution, solution and infusional set preparation, filling of the pumps), the time employed by four different nurses for at least twice a day for three days was recorded on a file. The average time was considered in the study.

### CIP™ pump

The device consists of two to four elastomeric pumps connected to a four-way disposable electronic control unit which independently manages drug flow according to a factory presetting scheme. The unit is powered by two alkaline AAA batteries that are included in the kit together with a specially designed bag. All the material is disposable. The cost of the kit was provided by H.S. Hospital Service S.p.A., Rome, Italy, which produces and merchandises the pump in the Italian market.

Pump preparation consisted of filling up four elastomeric pumps, one with oxaliplatin diluted with 5% glucose, one with folinic acid diluted with saline, one with 5-FU diluted with 5% glucose, and finally one with 5% glucose. Each pump contains 160 ml of solution. At the time of the study, pharmaceutical presentation of oxaliplatin and 5-FU was a liquid ready to be diluted, whereas folinic acid was in a powder form. Elastomeric pumps had to be connected to the CIP™ device from which depart four patient lines. Purging is controlled by the device as the first part of the infusional program. Purging lasted not more than one minute.

Pump preparation time was determined as stated above: the average time was considered in the study.

## Results

Costs for disposable materials, drug preparation, and patient care are summarized in Table 1.

### Traditional setting

*Disposable material costs.* Disposable materials consisted of one 500 cc bottle of 5% glucose solution, two 250 cc bottles of 5% glucose solution, two 500 cc bottles

**Table 1 - Direct costs for the administration of FOLFIRI or FOLFOX regimen according to a traditional setting or the CIP™ Pump**

Disposable material	Quantity	Cost per unit	Total cost
<b>Traditional</b>			
5% glucose 500 cc	1	0.46	€ 0.46
5% glucose 250 cc	2	0.40	€ 0.80
NaCl 500 cc	2	0.45	€ 0.90
NaCl 100 cc	3	0.35	€ 1.05
Elastomeric pump	1	26.22	€ 26.22
10 cc syringe	3	0.07	€ 0.21
Infusional set	2	1.98	€ 3.96
<b>Drug preparation</b>			
Pharmacist	Minutes 2	Cost/hr 42.00	€ 1.40
Nurse	20	19.00	€ 6.33
<b>Patient care</b>			
Medical examination day 1	15	47.00	€ 11.75
Medical examination day 2	5	47.00	€ 3.92
Nurse	300	19.00	€ 95.00
Inpatient pump	300	0.20	€ 1.00
Meal	1	6.00	€ 6.00
<b>Total</b>			<b>€ 159.00</b>
<b>CIP™ PUMP</b>			
NaCl 500 cc	1	0.45	€ 0.45
5% glucose 500 cc	1	0.46	€ 0.46
10 cc syringe	2	0.07	€ 0.14
50 cc syringe	4	0.25	€ 1.00
CIP™ pump	1	420.00	€ 420.00
<b>Drug preparation</b>			
Pharmacist	2	42.00	€ 1.40
Nurse	25	19.00	€ 7.92
<b>Patient care</b>			
Medical examination day 1	15	47.00	€ 11.75
Pump positioning	5	19.00	€ 1.58
<b>Total</b>			<b>€ 444.70</b>

of NaCl solutions, three 250 cc bottles of NaCl solutions, three 10 cc syringes, two infusional sets, and one elastomeric pump.

*Drug preparation.* Oxaliplatin, irinotecan and 5-FU dilution took not more than 2 min/pharmacist (42.00 euro/hour = 3.50 euro) and 4 min/nurse. Folinic acid dilution was more time consuming, accounting for about 6 min/nurse per day (for two days). Infusional set preparation took 2 min/nurse per day (for two days). Thus, nurse time for drug preparation was 20 min, for a final cost of 19.00 euro/hour = 6.33 euro.

*Patient care.* Medical examination for Day Hospital admission took 15 min, with an additional 5 min for day 2 check, for a total cost of 47.00 euro/hour = 15.67 euro.

Infusion of iv antiemetics, corticosteroids and gastric protector accounted for 30 min. Oxaliplatin or irinotecan are infused in 90 min, 5-FU bolus in 15 min per day (days 1 and 2), folinic acid in an additional 120 min per day (days 2 and 2), for a total patient care time of 390 min per cycle. As oxaliplatin and irinotecan might be infused with folinic acid contemporarily, we might reduce this time to 300 min per cycle. Thus, final computed cost was 19.00 euro/hr (nursing care) for 300 min = 95.00 euro.

Electronic inpatient pumps for the administration of iv drugs are frequently employed in Italian hospitals. The average cost of these pumps is 1,500.00 euro. Considering a utilization of 6 hr per day, 5 days a week, 50 weeks per year for a maximum of 5 years, pump cost is 0.20 euro per hour. Thus, electronic inpatient pump utilization was 1 euro (0.20 euro/hr for 5 hr).

Finally, patients submitted to chemotherapy in the traditional setting ate at our Day Hospital, with an additional cost of 6.00 euro.

On the whole, costs for a FOLFOX or a FOLFIRI regimen in a fully Day Hospital setting was 159.00 euro (Table 1).

#### *CIP™ costs*

*Disposable material cost.* Disposable materials consisted of one 500 cc bottle of 5% glucose solution, one 500 cc bottle of NaCl solution, four 50 cc syringes, two 10 cc syringes, and one CIP™ pump. The pump costs 420.00 euro (350.00 + 20% VAT).

*Drug preparation.* Oxaliplatin, irinotecan and 5-FU dilution took not more than 2 min/pharmacist (42.00 euro/hour = 3.50 euro) and 4 min/nurse. An additional 4 min were needed to fill the pump. Folinic acid dilution accounted for about 10 min and pump filling, 3 min. Pump setup accounted for 4 min. Thus, nurse occupation time for drug preparation was 25 min, for a final cost of 19.00 euro/hour = 7.92 euro.

*Patient care.* Medical examination for Day Hospital admission took 15 min, for a total cost of 47.00 euro/hour = 11.75 euro.

Pump positioning accounted for not more than 5 min/nurse for a cost of 1.58 euro.

Final cost for the CIP setting was 444.70 euro (Table 1).

## **Discussion**

The number of patients who need to be treated with a FOLFOX or a FOLFIRI regimen is growing. Data from the Tumor Registry of Torino confirm that colorectal cancer incidence in the town of Torino has increased from an adjusted rate of 45/year in 1985 to 57.5/year in 2005, with a 28% increase<sup>9</sup>. The trend has been constant since the late '70s, and it is reasonable to think that it will continue to increase in the near future. Thus, in 2008 we might expect more than 38,000 new cases in Italy, 19,000 of them with an indication to either FOLFOX or FOLFIRI chemotherapy<sup>10</sup>. Thus, colorectal cancer is becoming a social problem for its psychological, family, and working implications, but also for the public health costs. In the era of continuing cost savings, every aspect of these treatments should be carefully considered in order to minimize treatment costs<sup>9,11-17</sup>. Reduction of the time spent by patients in hospital represents a valid way to minimize costs, permitting a large num-

ber of patients who need more complicated treatment to find room in our busy oncologic units and thus increase the quality and quantity of care with comparable resources.

In our study, the CIP™ pump apparently had a higher cost. This is obviously true if we consider only the material needed to administer chemotherapy and the staff costs. However, it permitted a significant reduction of seat or bed occupation with a lower nursing and medical care time that can be estimated in a savings of about 100.00 euro. Thus, as regards materials and direct patient care, there was a balance of 258.70 euro in favor of the traditional administration. It should be noted that the traditional setting accounted for a seat occupation of at least 300 min with an additional 20 min for drug preparation, which was 10 times longer than the 30 min required by nurse for the CIP™ pump. This means that with the same resources we might treat 10 times as many patients with the CIP™ pump than with traditional infusion. Implications in work organization are easy to understand but they are not the focus of this paper. What is clearly evident is that general costs such as heating and climatization of hospital buildings, cleaning of the oncologic unit and of the common area of the hospital, garbage management, power supply and water costs, ordinary and extraordinary maintenance of the buildings, administrative and superstructure costs (such as the medical team ready to take immediate action in case of any emergency, the computer network system, etc.) would be split on a major number of patients. These general costs are fixed depending on the total room volume of the entire hospital, the number of buildings and how they are connected, the number of patients that can be hospitalized, and on several other variables.

These costs are the basis of the so-called "basic costs analyses", which is extremely complicated and not yet standardized<sup>18</sup>. In fact, these analyses have never been made in our structure, and it is evident that such costs differ according to the hospital (buildings in southern Italy have less heating costs than those in the northern part of the country, for example). In our study, hypothesizing that we might treat 5 patients with the CIP™ pump instead of 1 patient in the traditional setting, it is sufficient that the general costs for a single day hospital seat is more than 52.00 euro per cycle – which is easily the case in our Italian hospitals – to indicate the CIP™ pump as the more cost-saving methodology. Moreover, we should consider the growing number of patients who will benefit from these chemotherapy regimens, which will further lower this threshold as we might accept 5 more patients with the same nurse, medical and structural resources.

Acute oxaliplatin and irinotecan toxicity might represent a major problem for the administration of these drugs on an outpatient basis. Acute laryngeal spasm, immunomediated reactions, or acute cholinergic syn-

drome, although rare, are events that might occur<sup>19,20</sup>. It is up to the physician together with the patients to decide whether it is safe or not to deliver oxaliplatin or irinotecan in a fully ambulatory setting. It should be noted that these acute events are typical in the same patient and are recorded immediately. Thus, it could be a good compromise to administer the first two cycles in a more traditional way and, just in case no acute event is recorded, to continue on a fully outpatient basis.

The administration of oxaliplatin or irinotecan on an inpatient basis and folinic acid and 5-FU on an outpatient basis increased the total cost of the CIP™ pump by 28.50 euro (90 min of nurse/care at a cost of 19.00 euro/hour). Even though this is not the best solution for minimizing costs, it might be a better way, even from a pharmacoeconomic point of view, to administer FOLFOX or FOLFIRI instead of the traditional way, increasing the general cost threshold by no more than 6.00 euro. This should be preferred by oncologists who are not confident with the administration of oxaliplatin and irinotecan on an outpatient basis, as it reduces social costs.

Last but not least, it is noteworthy that fully ambulatory pumps can reduce indirect costs such as work capacity reduction, and intangible costs such as a lower impact on the global patient quality of life. In fact, several patients are active in their social life and many of them continued to work during therapy administration<sup>7</sup>.

In conclusion, material and staff costs for the CIP™ pump are higher than for traditional chemotherapy administration. However, even not considering indirect and intangible costs, CIP cost-saving surpassed traditional infusion when considering general costs and will be more and more indicated in the future as patients who will benefit from a FOLFOX or FOLFIRI regimen will grow in number and there are no more resources to widen the Public Health offer.

## References

- Pickering L, Rudman S, Ross PJ, Leslie MD: Targeted therapy in colorectal carcinoma: more than a theory. *Colorectal Dis*, 10: 218-221, 2008.
- Malvezzi M, Bosetti C, Negri E, La Vecchia C, Decarli A: Cancer mortality in Italy, 1970-2002. *Tumori*, 94: 640-657, 2008.
- Capocaccia R, Buzzoni C, Grande E, Inghelmann R, Bellù F, Cassetti T, de Dottori M, Donato A, De Lisi V, Falcini F, Federico M, Ferretti S, Fusco M, Giacomini A, Guzzinati S, Mangone L, Piffer S, Rosso S, Sechi O, Tagliabue G, Tumino R, Vercelli M, Vitarelli S: Estimated and observed cancer incidence in Italy: a validation study. *Tumori*, 93: 387-391, 2007.
- Meyerhardt JA, Mayer RJ: Systemic therapy for colorectal cancer. *N Engl J Med*, 352: 476-487, 2005.
- Pinedo HM, Peters GJ: Fluorouracil: biochemistry and pharmacology. *J Clin Oncol*, 6: 1653-1664, 1988.
- Diasio RB, Harris BE: Clinical pharmacology of 5-fluorouracil. *Clin Pharmacokinet*, 16: 215-237, 1989.
- Tampellini M, Bitossi R, Brizzi MP, Saini A, Tucci M, Alabiso I, Dogliotti L: Pharmacoeconomic comparison between chronochemotherapy and FOLFOX regimen in the treatment of patients with metastatic colorectal cancer. A cost-minimization study. *Tumori*, 90: 44-49, 2004.
- Tournigand C, Andre T, Achille E, Lledo G, Flesh M, Mery-Mignard D, Quinaux E, Couteau C, Buyse M, Ganem G, Landi B, Colin P, Louvet C, de Gramont A: FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. *J Clin Oncol*, 22: 229-237, 2004.
- Piedmont Cancer Registry. Epidemiology of colorectal cancer [Internet]. Torino (Italy): Centro di Riferimento per l'Epidemiologia e la Prevenzione Oncologica in Piemonte [Updated 2009; cited 11 may 2009]. Available from: <http://www.cpo.it/dationcologi/rt09.htm>
- AIRTUM Working Group: Documento annuale 2009 - I nuovi dati di incidenza e mortalità periodo 2003-2005 [Internet]. *Epidemiologia e Prevenzione*, anno 33 (1-2) gennaio-aprile 2009 supplemento 2. Available from: [http://www.registri-tumori.it/cms/files/AIRTUM\\_Incidenza.pdf](http://www.registri-tumori.it/cms/files/AIRTUM_Incidenza.pdf)
- Levy-Piedbois C, Durand-Zaleski I, Juhel H, Schmitt C, Bellanger A, Piedbois P: Cost-effectiveness of second-line treatment with irinotecan or infusional 5-fluorouracil in metastatic colorectal cancer. *Ann Oncol*, 11: 157-161, 2000.
- Ross P, Heron J, Cunningham D: Cost of treating advanced colorectal cancer: a retrospective comparison of treatment regimens. *Eur J Cancer*, 32A: S13-S17, 1996.
- Sculpher M, Palmer MK, Heyes A: Costs incurred by patients undergoing advanced colorectal cancer therapy. A comparison of raltitrexed and fluorouracil plus folinic acid. *Pharmacoeconomics*, 17: 361-370, 2000.
- Focan C: Pharmaco-economic comparative evaluation of combination chronochemotherapy vs standard chemotherapy for colorectal cancer. *Chronobiol Int*, 19: 289-297, 2002.
- Jansman FG, Postma MJ, Brouwers JR: Cost considerations in the treatment of colorectal cancer. *Pharmacoeconomics*, 25: 537-562, 2007.
- Tappenden P, Jones R, Paisley S, Carroll C: Systematic review and economic evaluation of bevacizumab and cetuximab for the treatment of metastatic colorectal cancer. *Health Technol Assess*, 11: 1-128, 2007.
- Tappenden P, Jones R, Paisley S, Carroll C: The cost-effectiveness of bevacizumab in the first-line treatment of metastatic colorectal cancer in England and Wales. *Eur J Cancer*, 43: 2487-2494, 2007.
- Adam T, Evans D, Murray C: Econometric estimation of country-specific hospital costs. *Cost Eff Resour Alloc* 1: 3, 2003. Available from: <http://www.resource-allocation.com/content/1/1/3> (accessed May 11, 2009)
- Leonard GD, Wright MA, Quinn MG, Fioravanti S, Harold N, Schuler B, Thomas RR, Grem JL: Survey of oxaliplatin-associated neurotoxicity using an interview-based questionnaire in patients with metastatic colorectal cancer. *BMC Cancer*, 5: 116, 2005.
- Jansman FG, Sleijfer DT, de Graaf JC, Coenen JL, Brouwers JR: Management of chemotherapy-induced adverse effects in the treatment of colorectal cancer. *Drug Safety*, 24: 353-367, 2001.