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The CAP-CR study: Direct medical costs in Italian metastatic colorectal cancer patients on first-line infusional 5-fluorouracil or oral capecitabine

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ABSTRACT

Aim: To describe the healthcare resource consumption of metastatic colorectal cancer (MCRC) patients in the Italian healthcare setting.

Methods: A retrospective chart analysis estimating direct medical costs of first-line infusional 5-Fluorouracil (5-FU) or oral Capecitabine (CAP), associated or not with other chemotherapies, from the Italian Healthcare Service (IHCS) and Hospital (H) perspectives.

Results: 202 subjects were analysed. CAP patients ($N = 66$) were older, with a more compromised clinical status and received less chemotherapy agents in association than 5-FU patients ($N = 136$). From the IHCS perspective, mean total costs per patient were €12,029 and €5,781 in the 5-FU and CAP arms respectively; €7,338 and €4,688 from the H perspective. The infusional administration route of 5-FU was a cost driver from both perspectives. Sensitivity analyses found the results to be robust to variations in base case parameters.

Conclusions: Management of MCRC by oral chemotherapies may be an economically advantageous option to both IHCS and hospitals.

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1. Introduction

Colorectal cancer (CRC) is one of the most frequent and lethal carcinomas: in Western countries about 8% of total cancer deaths are due to CRC with one subject in twenty being affected.¹ Standardised rates place Italy on lower-middle levels over the European population for both incidence (29.46 cases/100,000/year) and mortality (12.32 deaths/100,000/year).¹ Na-

tional registries show that in Italy frequency rates of CRC are higher in northern regions compared with southern regions;^{2,3} survival rates indicate that about 40–60% of subjects survive for 3/5 years after their diagnosis, depending on the carcinoma site.³

CRC therapy treatments include surgery, chemotherapy, radiation or a combination.⁴ Chemotherapy represents the golden standard for CRC treatment and the efficacy of differ-

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ent protocols varies according to drug combinations: 5-fluorouracil (5-FU) - infusional or in bolus - has demonstrated to be highly effective in the treatment of CRC; its association with levofolinate has been shown to increase the clinical response; the association with irinotecan and oxaliplatin has been proven to increase survival.^{5,6} AIOM (Italian Association of Medical Oncology) guidelines suggest that 5-FU, preferably infused, should be administered as politherapy; its substitution with oral capecitabine (CAP) is possible when 5-FU is administered as monotherapy or in association.^{4,7} CAP, an orally administered fluoropyrimidine, as single-agent therapy, has shown to be highly effective in the first-line treatment of metastatic CRC, with lower toxicity rates of diarrhoea, stomatitis, nausea and neutropenia.⁸ The efficacy, tolerability and ease of administration makes it appropriate for use in the general CRC population and in elderly patients who are more likely to experience the inconvenience and discomfort of frequent hospital visits for intravenous drug administration, often associated with a high risk of infection.⁸

Studies estimating the social burden of CRC are scant in the Italian literature. One study estimated that the full monthly hospital cost of CRC varies according to the therapeutic scheme adopted: €2,600 in the CPT-11 raltitrexed scheme and €200 per Mayo clinic 375 regimen.⁹ Costs of chemotherapy schemes including 5-FU in association with irinotecan, with or without levofolinate, are in the range of €1,100–€2,900 per treatment cycle while the association with oxaliplatin ranges between €1,298 and €2,374 per cycle.¹⁰ The use of oral CAP, in association with oxaliplatin, may therefore be advisable under an economic point of view since its administration route could represent a cheaper option than infusional chemotherapy in the treatment of metastatic CRC.

The objective of this study was to describe the healthcare resource consumption of patients affected by metastatic CRC receiving first-line chemotherapy with infusional 5-FU or oral CAP, in association or not with levofolinate, oxaliplatin and irinotecan.

2. Patients and methods

This was a retrospective analysis on patients' medical charts. Data were collected among five oncology centres representative of the Italian current practice in the treatment of CRC. Adult (>18 years) patients, affected by metastatic CRC, who had received and completed by 30 November 2006 a first line chemotherapy with oral CAP or 5-FU - also in association with other chemotherapeutic agents - were included in the analysis. The study protocol was approved by Ethics Committees of all participating centres and patients were requested to give their written consent to personal data treatment prior to the study beginning. Patients were excluded from the analysis in case of: concomitant participation to clinical studies, ab-

sence of informed consent and loss to follow-up, with the exception of chemotherapy interruption due to adverse events, toxicity or death. Authorised users had to input the data into a MS SQL/Server database through a web application with online control functions. Demographic, anamnestic and chemotherapy information were collected for each treatment cycle and included details on ECOG performance status, specialist visits, diagnostic tests, treatment dosages, planned and performed cycles, possible variations in chemotherapy schemes and reasons for changes, onset of adverse events (due to chemotherapy or administration route) and resource consumption due to their management.

2.1. Statistical and cost analysis

The sample was analysed by gender, age, time since diagnosis, chemotherapy type and possible variation of schemes, ECOG performance status, concomitant diseases, frequency of adverse events and deaths.

Direct medical costs (chemotherapy drugs, administration, infusional device insertion, supportive therapy, standard laboratory tests and adverse events management) were estimated via the perspective of the Italian Healthcare Service (IHCS)^h and the Hospital (H).

For each centre and treatment line, the total cost of treatment and the mean cost per patient were calculated; costs of drugs, administration type and adverse events management are presented separately according to the considered perspective. The total cost per treatment was estimated by summing up each patient cost. The mean per patient cost was estimated as the ratio between total treatment costs and the number of subjects in each study group.

Resource consumption was valued according to the adopted perspective: national tariffs in the IHCS perspective, market retail prices and full costs in the H perspective (2007 values). The costs of supportive drugs and adverse events/complications (Table 1) - which represented a marginal component in the analysis - were, as a proxy, costed equally in both perspectives,¹¹ given the difficulty of retrieving full hospital costs. The cost of infusion device implant was only included if the procedure was performed at the study centre. Administration costs refer to the therapeutic pattern of patients undergoing chemotherapy: 5-FU was administered in the day hospital (DH) setting (one access per day of infusion) and CAP in the outpatient setting (one visit per cycle).

All drugs registered in the data collection were valued by IHCS price if used in the inpatient setting, and by retail price if used at patients' domicile. A review of regional decrees showed that CAP, oxaliplatin and irinotecan are reimbursed besides the DRG tariff; therefore, the cost of these therapies was added to the DRG tariff when using the IHCS perspective. As far as 5-FU is concerned, the lowest price per mg was

^h In Italy, healthcare services and costs are managed by the IHCS which is regionally based. Secondary care includes specialised ambulatory services such as visits, diagnostic and curative activities (i.e. infusional chemotherapies, etc.). The IHCS applies ambulatory tariffs to visits, procedures or services delivered in this setting. Tertiary care refers to hospital care; hospitals contracting with the IHCS are funded on the basis of the DRG system (in force since 1996). DRGs are assigned by a 'grouper' programme based on ICD diagnoses, procedures, age, sex, and the presence of complications or comorbidities, based on the idea that patients within each category are clinically similar and are expected to use the same level of hospital resources. For each generated DRG, the IHCS pays hospitals a lump sum which should cover hotel, procedures, drugs and labour costs.

Table 1 – List of unit costs

Item	IHCS Perspective	H Perspective	Sources
<i>Chemotherapy drugs (€/mg)</i>			12
Fluorouracil	0.002	0.002	
Capecitabine	0.006	0.006	
Irinotecan	1.024	1.024	
Oxaliplatin	3.711	3.711	
Levofolinate	0.093	0.093	
Specialist visits	20.66	20.66	13
<i>Adverse events</i>			
DH			14
Anaemia (DRG 395)	279.92	279.92	
Diarrhoea, dehydration (DRG 297)	240.15	240.15	
Skin infection (DRG 278)	218.46	218.46	
Full hospitalisation			14
Intestinal occlusion (DRG 181)	1792.62	1792.62	
Neutropenia (DRG 399)	2910.23	2910.23	
Diarrhoea and mucositis (DRG 183)	1742.01	1742.01	
Abdominal pain (DRG 171)	3925.07	3925.07	
<i>Infusional administration</i>			
Insertion of central venous catheter or port-à-cath	300.06 ^a	628.36	14,15
Central venous catheter device	.. ^b	345.70	16
Port-à-cath device	.. ^b	403.00	16
<i>Chemotherapy</i>			
Infusional chemotherapy	413.99 ^c	9.18 ^d	14,17
Elastomeric pump device	.. ^b	40.00	15
Oral chemotherapy	20.66	3.79 ^e	13,15
ICHS – Italian Healthcare Service; H – Hospital. a DRG 466 – DH regimen; only Padua Hospital used the DRG 173 (full hospitalisation regimen – €3,647). b Included in the DRG tariff. c DRG 410 – DH regimen. d Full cost of equipment and personnel. e 10 min working time of a hospital pharmacist.			

adopted, in a conservative hypothesis. Table 1 details main unit costs and relative sources from each perspective; the full list may be requested from the authors. Two sensitivity analyses were performed:

1. in both perspectives, the cost of central venous catheter was estimated on the whole 5-FU sample assuming that subjects included in the analysis received the device insertion at the study centres;
2. in the IHCS perspective, the DRG tariff for chemotherapy infusion - which differs at regional level - was varied from the national value (€414) of the base case, to the lowest (€138 for the Veneto region)¹⁸ and highest value (€604.93 for the Piemonte region).¹⁹

3. Results

The analysis included 202 metastatic CRC patients (136 on infusional 5-FU treatment and 66 on oral CAP). Patients' characteristics are summarised in Table 2. The two clusters showed some demographic differences, with the exclusion of gender (both groups showed a prevalence of males). CAP patients were older ($p < 0.0001$, χ^2 test) which may be attributable to the administration route that did not require constant, regular access to oncology departments for infusions like the case of 5-FU. Anamnestic and clinical variables also suggested

that CAP patients had a more compromised clinical status: time since diagnosis was 55.91 weeks in the CAP arm versus 41.99 weeks of the 5-FU group; moreover, 56% of CAP patients presented concomitant disease versus 25% of the 5-FU arm. ECOG scores at baseline showed that a higher number of CAP patients suffered from restrictions in physical activities or movements compared to 5-FU treated patients (Table 2). There were 95 deaths - mostly in the 5-FU arm - due to cancer progression, generally occurring 2 years after the last chemotherapy cycle. In both groups, metastases were mostly localised in the liver.

3.1. Chemotherapy

In all centres, duration of CAP therapy was 21 days (14 treatment days followed by a 7-day no treatment interval). The total duration of 5-FU chemotherapy varied across centres: 14, 15, 21 or 28 days, of which the actual days of infusion were 2 or 3, with an interval of 11–25 days. Furthermore, in some patients, the 5-FU scheme scheduled a single dosage at the first day or a consecutive 7-days dosage. 5-FU was associated to other chemotherapies in 92.6% of patients versus 47.0% of the CAP arm. Table 3 reports details on the number of planned and performed cycles as well as chemotherapy dosages in the two arms. As shown in the table, CAP planned cycles were almost entirely performed compared with cycles in the 5-FU arm. Almost all 5-FU patients received infusion by central ve-

Table 2 – Population characteristics

	5-FU infusional	CAP oral
<i>Patients</i>		
N	136	66
Male/female (%)	55/45	61/39
Age (years): mean (SD)	62.5 (8.0)	72.1 (9.5)
Deaths (%)	74.7	25.3
<i>Concomitant diseases (%)</i>		
Patients with at least one concomitant disease	25.0	56.1
Cardiovascular	64.7	70.3
Metabolic	29.4	18.9
Urogenital	11.8	16.2
Central nervous	8.8	8.1
Digestive	2.9	18.9
Respiratory	2.9	5.4
Muscle skeletal	0	5.4
Other	8.8	8.1
<i>Weeks since first diagnosis</i>		
N (mean)	42.0	55.9
<i>Metastasis (%)^a</i>		
Liver	70.6	66.7
Lung	16.2	28.8
Soft tissues/skin	11.8	7.6
Bone	1.5	4.6
Other	28.7	25.8
<i>ECOG score</i>		
0 – full active (%)	60.3	34.9
1 – restricted in physical activity (%)	37.5	57.6
2 – bed or chair bound up to 50% of waking hours working time (%)	2.2	7.5

a Patients could present one or more metastasis.

Table 3 – Number of cycles and chemotherapy dosages per patient

	5-FU infusional	CAP oral
<i>Cycles (mean)</i>	N	N
Total planned	10.7	6.7
Total performed	9.7	6.4
<i>Chemotherapy (mean, min-max)</i>	mg	mg
Total in the study	34,781 (2400–74,964)	251,555 (28,000–588,000)
<i>Drugs in association</i>		
Total oxaliplatin	1524 (152–2544)	1389 (840–2520)
Total irinotecan	1791 (400–3888)	537 (400–800)
Total levofolinate	3680 (0–10,342)	–

nous catheter: 47% required a hospital admission for catheter insertion, whilst 72 of them were already implanted. Infusional pumps were of 24 h elastometric type in 80% of patients and port-à-cath in 20% of cases.

3.2. Adverse events

More patients in the 5-FU group than the CAP group (50.7% versus 33.3%) suffered from an adverse event or complication due to chemotherapy or an infusional route. In particular, 48.5% of 5-FU patients showed at least one adverse event due to chemotherapy compared to 33.3% of CAP patients. In both clusters, nearly 16% of patients reported an adverse event which required a variation of chemotherapy. Adverse events determined chemotherapy interruption in 7–8% of

cases in both arms; however, the main reason for chemotherapy withdrawal was cancer progression (12–13% in both arms).

On average, 2.14 events per 5-FU-patient and 1.68 events per CAP-patient were observed. Thrombocytopenia was the most frequent event in the 5-FU arm (40.5% versus 13.5%), whilst diarrhoea was the most frequent event observed in the CAP arm (18.9% versus 8.1%). Other events (neutropenia, anaemia, and leucopenia) were negligible. Events associated to the central venous catheter were: hypersensitivity reaction (46.2%), superficial fleabite or obstruction (15.4%), stoma problems, granulomas or infections (7% each). The frequency distribution of adverse events analysed by type of treatment and by age did not show any statistical difference ($p = 0.1730$, Cochran Mantel Haenzel test).

3.3. Cost analysis results

From the IHCS perspective, mean total cost was €12,029 (SD €5521) per 5-FU-patient versus €5781 (SD €4933) per CAP-patient. Considering only patients in combination regimens, mean total costs per patient were €12,534 in the 5-FU plus oxaliplatin or irinotecan arm and € 9986 in the CAP plus oxaliplatin or irinotecan arm. The main cost difference between the two arms was due to the 5-FU administration type (infusional) which required a higher number of DH accesses for

a total of €6000 versus €1600 in the CAP arm. Drug costs – including associated chemotherapeutic agents - amounted to €4433 and €3471 in the 5-FU and CAP arms respectively (Fig. 1).

From the hospital perspective, mean total cost was €7338 (SD €4306) per 5-FU-patient versus €4688 (SD €3552) per CAP-patient. Again, the two strategies showed differences in the administration route costs (€720 for 5-FU versus €194 for CAP) due to the number of H accesses for infusion in the 5-FU arm (Fig. 2). From both perspectives, alternatives differed as to costs of catheter insertion, adverse event management

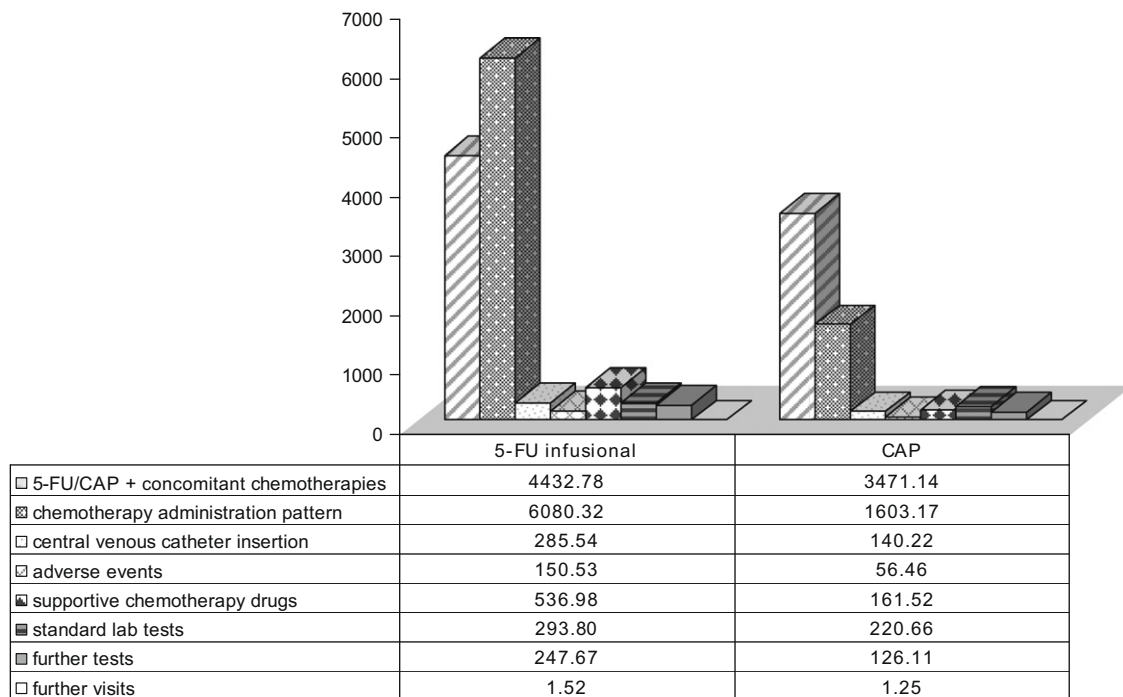


Fig. 1 – Mean per patient cost (€) – Italian Healthcare Service perspective.

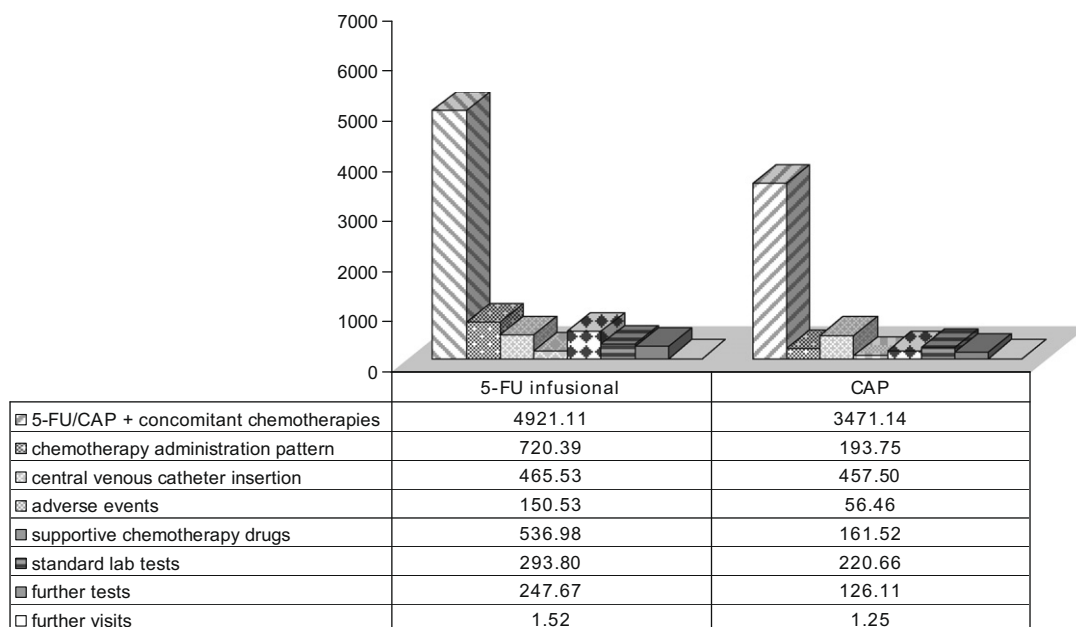


Fig. 2 – Mean per patient cost (€) –Hospital perspective.

Table 4 – Sensitivity analysis (costs in €)

	5-FU infusional		CAP oral	
	IHCS perspective	H perspective	IHCS perspective	H perspective
<i>Basecase^a</i>				
Total mean cost per patient	12,029	7338	5781	4688
<i>Sensitivity analysis</i>				
Central venous catheter implanted on the whole 5-FU sample (N = 136)	12,250	7853	–	–
Highest DRG tariff for chemotherapy (€604.93, Piemonte region)	14,833	–	6487	–
Lowest DRG tariff for chemotherapy (€138, Veneto region)	7975	–	4876	–
a Cost components: National DRG tariff (€414) for chemotherapy, central venous catheter implanted at the study centre (N = 64).				

and chemo-supportive therapy, which were negligible anyway (1–7% of total costs in both arms).

Table 4 shows results for the sensitivity analyses. The average per patient cost did not significantly vary when inputting all costs of catheter insertion: the IHCS would spend on average an additional €220 per patient and the H about €500 per patient. On the contrary, the DH DRG tariff for chemotherapy was the cost driver: if the IHCS applied the lowest tariff, it would save €4000 per patient. From both perspectives, the mean total per patient cost was always lower in the CAP arm compared with the 5-FU group.

4. Discussion and conclusions

Current chemotherapy of metastatic CRC is based on 5-FU, continuous infusion or bolus, sometimes in association with leucovorin.^{4–6} It is commonly known in the medical community that, despite proven clinical efficacy, 5-FU infusion is often associated with medical complications (infections and bleeding), functional problems (occlusion of the central catheter, need of regular cleaning of the central venous access by specialised personnel), relevant healthcare costs and poor patient quality of life (need of hospitalisation, discomfort due to frequent transfer to centre care).²⁰ The availability of oral therapies with demonstrated clinical efficacy and safety may therefore represent a valid alternative in the management of metastatic CRC. Moreover, it could show potential economic advantages for the H and the IHCS mainly deriving from reduction in infusional costs and adverse events management.

Our analysis estimated that, both from the IHCS and H perspectives, the difference in costs between 5-FU and CAP is not determined by the central venous catheter insertion nor by chemotherapy adverse events management, but by the administration route (infusional and oral respectively). The oral administration would enable the IHCS and the H to save €6250 and €2649 respectively. From the IHCS perspective, drug cost weighted for 37% on the mean per patient cost in the infusional arm and for 60% in the oral arm: in the 5-FU arm, 51% of this cost was attributable to the management of infusional therapy versus 28% of the CAP arm. The DH DRG tariff for chemotherapy infusion (€414 at the national level) resulted in being the cost driver from the IHCS perspective: sensitivity analyses showed that when the lowest tariff was used

(€138 in the Veneto region), then the cost of the infusion accounted for only 25% of the mean per patient cost, narrowing the difference between the two arms by about €3000 (€7975 versus €4875 respectively). Nevertheless, the oral administration route remained the less costly: our results showed that the DRG tariff for infusional chemotherapy has always had a high impact on IHCS expenditure even when considering the lowest cost.

Furthermore, from the H perspective, the study estimated that oral CAP administration led to a saving of €2650 versus the infusional alternative: although drugs cost weighted for 74% in the CAP arm and 67% in the 5-FU arm, the cost of infusional management - in terms of device use and personnel labour - amounted respectively to 4% and 10% of total costs.

Our results are comparable to findings from another Italian study evaluating costs of oral CAP versus infusional 5-FU in the management of metastatic CRC.²¹ The study estimated that the IHCS could save €1600 per year when using oral chemotherapeutic agents compared to infusional chemotherapy. Also in this study, the cost driver in the CAP arm was represented by chemotherapy while the administration route cost was the driver in the 5-FU arm.²¹ A recent French retrospective study estimated savings for the healthcare service in the range of €2000–€7200 when using a simpler 5-FU regimen (in association with oxaliplatin or irinotecan) instead of the de Gramont standard scheme.²² A UK Health Technology Assessment estimated savings in the range of £1300–£4100 (€1600–€5100) for the health service when CAP was used in substitution of a modified 5-FU de Gramont dosage scheme.²³

Different findings are reported by a recent Editorial in the Journal of Clinical Oncology.²⁴ According to the author, the substitution of 5-FU with CAP in combination with oxaliplatin, in various schemes, is justifiable only if clinical outcomes, safety profiles and costs are very similar. The author estimated that over a 12-week period the cost for treating metastatic CRC patients with CAP increased by threefold compared with two different 5-FU schemes in combination with oxaliplatin.²⁴ Differences in drug costs between Mayer's work and our analysis could be explained by the higher amount of CAP per cycle considered in the Editorial: 50,400 mg versus 36,600 mg. Indeed, clinicians of participating centres confirmed that chemotherapy drugs were used, mainly in older people, at lower dosages and for an inferior

number of cycles than in published clinical trials. Furthermore, this discrepancy may be attributable to the higher price of capecitabine in the US. Most notably, apart from differences in dosages and prices, this work highlights the fact that therapy cost is a wider concept than mere drug cost and other cost components - such as administration costs - could be more relevant in the decision making process which represents a balance between therapy efficacy and safety, patients' characteristics and preferences, and costs.²⁵

There are some limitations in this study. The number of patients differs in the two groups: 136 in the 5-FU arm versus 66 in the CAP group. This discrepancy may be due to the fact that in the Italian clinical practice the treatment of metastatic CRC with oral CAP is less commonly used than the gold standard 5-FU chemotherapy.

We attempted to provide a hospital perspective, retrieving information on full hospital costs from published literature and using tariffs - as a proxy - when these were not available. Indeed, additional studies are necessary for a more accurate estimate. However, we think that the results shown here represent a starting point to further explore the economic burden of infusional chemotherapy.

Finally, it was not possible to collect patients' preferences. International studies report that patients affected by terminal CRC prefer receiving tablets rather than infusional chemotherapy.^{20,26,27} A recent Italian article demonstrated that 34 out of 59 advanced breast cancer patients preferred the oral administration route because it reduced the disease perception (77%) and improved coping with it (67%). These preferences were much more relevant in younger (<45 years) patients.²⁸ Our study does not support this evidence: in the Italian clinical practice, the older and more health-compromised subjects receive the oral administration because of its lower toxicity and ease of administration. These conflicting results suggest the need to better identify the target population for the oral administration route, also with the aim of reducing healthcare costs.

In conclusion, although not fully exhaustive, this analysis - based on real Italian clinical practice data - supports evidence of lower management costs, both from the perspective of the IHCS and the H, when patients affected by metastatic, advanced CRC are treated with oral chemotherapy instead of infusional regimens.

Conflict of interest statement

None declared.

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