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Cost-Effectiveness Analysis of First-Line Chemotherapies in Metastatic Colorectal Cancer

Results of the Fédération Francophone de Cancérologie Digestive (FFCD) 9601 Randomized Trial

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Key Words
Metastatic colorectal cancer · Randomized trial · Cost-effectiveness analysis · Raltitrexed

Abstract

Background: The De Gramont regimen (or high-dose LV5FU2, HD-LV5FU2) is considered a standard treatment for metastatic colorectal cancer. The aim of the study was to evaluate the efficacy and the costs of three regimens as compared to HD-LV5FU2: raltitrexed (R), LV5FU2 with a lower dose of folinic acid (LD-LV5FU2), and weekly infusional 5FU (WI-FU). ***Methods:*** An economic analysis was performed prospectively as part of a randomized trial comparing first-line chemotherapy regimens in 294 patients with unresectable metastatic colorectal cancer. The primary endpoint was event-free survival (EFS). Direct medical costs were computed from the health system viewpoint using 2001 unit costs. ***Results:*** None of the three regimens improved EFS as compared to HD-LV5FU2. R was less effective and more toxic. The mean total cost per patient was € 15,970 for HD-LV5FU2. The cost of R (€ 10,687) was lower than that of HD-LV5FU2 ($p = 0.008$). The cost of LD-LV5FU2 (€ 14,888) and of WI-FU (€ 13,760) was not significantly different from that of HD-LV5FU2. ***Conclusion:*** The lower efficacy and increased toxicity of R made it a clinically inferior regimen despite its easy administration and lower cost. The HD-LV5FU2 protocol remains a better treatment. LD-LV5FU2 appeared a good alternative regimen because it reduced costs without jeopardizing its efficacy. The WI-FU regimen did not show a significant difference in terms of efficacy, but suggested toxicity to be slightly increased.

Introduction

In 2004 in Europe, there were an estimated 376,400 incident cases of colorectal cancer and 203,700 cancer deaths [1]. Approximately 50% of these patients will develop metastatic disease, for which the 5-year survival rate is less than 5%. Treatment of patients with metastat-

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ic disease may consist of palliative cytotoxic chemotherapy, which prolongs time to progression and survival [2] and is cost-effective compared to the best supportive care [3]. In France, the LV5FU2 regimen, the so-called De Gramont schedule, is considered a standard treatment for metastatic colorectal cancer as it showed it was more effective in terms of overall response (32.6 vs. 14.5%, p = 0.0004), event-free survival (EFS) (median 27.6 vs. 22 weeks) and less toxic (grade 3–4 toxicity: 11.1 vs. 23.9%) than the monthly Mayo regimen (infusion of 20 mg/m^2/day of folinic acid and 425 mg/m^2/day of 5FU for 5 days every 28 days) [4].

A large randomized EORTC trial showed that high-dose 5FU given as a weekly 24-hour infusion was better tolerated than bolus 5FU + FA without any advantage in terms of survival or EFS [5]. This regimen is now used in routine practice in Germany.

Tomudex® (raltitrexed, AstraZeneca) is the first agent of a new generation of thymidylate synthetase inhibitors, which allowed a simple administration schedule of 3 mg/m^2 once every 21 days. It was compared to the Mayo schedule in a phase III trial of metastatic colorectal cancer: EFS was not statistically different between the two arms, but raltitrexed resulted in less neutropenia and mucitis [6].

Treatment and care of colorectal cancer are estimated to account for approximately 2% of all bed days and between 10 and 20% of palliative care provision in the UK [7]. In 1996, it was estimated that 22 million Euros were spent on medicines for this disease (including cytotoxic chemotherapy and others drugs) in the UK [8]. Hospitalization care for colorectal cancer amounted to around 470 million Euros in France in 1999. Costs of colorectal cancer totaled 555.5 million Euros for the National Health System and 997 million Euros for society in general [9]. With a growing awareness that healthcare resources are scarce, it is therefore important to compare effectiveness in terms of clinical and cost outcomes [10]. Some economic analyses previously evaluated the cost-effectiveness ratios of chemotherapy regimens used for the primary treatment of advanced colorectal cancer in several countries [11–14]. They demonstrated that the LV5FU2 regimen was significantly more expensive than Mayo, Lokich and raltitrexed regimens. But these studies present some methodological limitations because the data collection was retrospective and included only patients for whom the data collection could be completed. The present study was then designed to collect resource utilization and costs prospectively alongside the trial for each patient, in parallel with clinical data.

The aim of the study was to evaluate the cost-effectiveness of raltitrexed, a LV5FU2 regimen with a lower dose of FA (low-dose LV5FU2) and weekly 5FU in first-line treatment of patients with metastatic colorectal cancer versus the De Gramont regimen (high-dose LV5FU2). Data were extracted from the multicenter randomized controlled trial sponsored by the Fédération Francophone de Cancérologie Digestive, FFCD 9601 trial, which evaluated the effectiveness and costs of these regimens in normal clinical practice.

Materials and Methods

Study Population

Patients were randomized between March 1997 and March 2001. They all had unresectable metastatic adenocarcinoma of the colon or rectum. Patients were allowed to have received adjuvant cytotoxic chemotherapy which had to be finished >6 months before entry on the study.

Treatment

Patients were randomized to receive one of four regimens:

(1) High-dose LV5FU2 (HD-LV5FU2): administered every 2 weeks for 2 consecutive days in an infusion of 200 mg/m^2 of folinic acid followed by a bolus of 400 mg/m^2 of 5FU over 10 min followed by a continuous 22-hour infusion of 600 mg/m^2 of 5FU. This was the reference arm that was compared to three other regimens:

(2) Low-dose LV5FU2 (LD-LV5FU2): same protocol as HD-LV5FU2 with FA at 20 mg/m^2 instead of 200 mg/m^2.

(3) Weekly 5FU: weekly continuous intravenous 24-hour infusion of 5FU at 2,600 mg/m^2 on day 1 for 6 weeks with 1 week of rest between cycles.

(4) Raltitrexed (Tomudex®, AstraZeneca): 3 mg/m^2 as a short intravenous infusion every 3 weeks.

The patients were treated until disease progressed or WHO grade 3 or 4 toxicity occurred in two cycles.

Endpoint

The primary endpoint was EFS, defined as the time from randomization to the date of the first event (disease progression or death) or to the date of the last follow-up for patients who had no event. The secondary endpoints were overall survival (OS) and grade 3–4 toxicities.

Definition of Costs

Costs were computed from the viewpoint of the healthcare system. We calculated the total cost of treatment of each patient, including costs from randomization until disease progressed or death or up to the date of the last follow-up for patients who had no event (min. 30.0 months, max. 36.7 months), by using 2001 reference costs. All volumes of resource utilization were collected for each patient prospectively alongside the trial in parallel with clinical data, except for the volumes related to transport and follow-up.

Table 1. Follow-up schedule recommended in the protocol and costs (according to the French National Health System)

Follow-up test	At randomization	Every 8 weeks	Before each cycle	Blood tests before each chemotherapy infusion
Consultation	×	×	×	
Hematology tests	×	×	×	×
Biochemistry tests	×	×	×	
Carcinoembryonic antigen	×	×	×	
Chest x-rays	×			
CT scan	×	×		
Electrocardiogram	×			
Total, Euros	326.26	277.66	98.6	10.8

Healthcare costs included: (1) drugs and hospital stays for the administration of chemotherapy; (2) follow-up (visits, biology, radiology); (3) hospitalizations for the management of complications or toxicities, and (4) patient transport costs.

Cost of Hospitalizations. The hospital stay with the reason for admission, the type of hospitalization (inpatient/outpatient), the type of unit and the duration of the stay were collected prospectively. The costs of hospital stays were extracted from the hospital cost accounting systems. The trial was conducted in four types of hospitals: hospitals specialized in cancer treatment, university hospitals, general hospitals, and private hospitals. We used a cost per day and per type of unit (oncology, surgery, intensive care, and day ward units) which was estimated as the mean of the two largest centers in each type of hospital. It included direct medical costs (medical supplies, laboratory tests, radiology), overheads and logistics costs, and represents actual costs (not those charged to the payer, i.e. National Health System).

The cost of hospitalization at home was estimated at € 140 per day (without chemotherapy drug acquisition cost) [15, 16].

Cost of Follow-Up. We took into account of the scheduled visits, biological and radiological examinations recommended in the protocol (table 1). The French National Health System reimbursement prices were used to valorize the visits and examinations [17].

Drug Costs. The dose and the number of cycles of chemotherapy were collected prospectively for each patient. We considered the actual daily prescription per drug and per patient. Drug costs were calculated by estimating the number of vials needed to provide the required dose for each infusion and each drug. To value the resources, we used the mean of the unit prices of vials obtained from the clinical pharmacy services of the two largest centers in each type of hospital.

The costs of drugs used for the treatment of complications and toxicity were estimated by using the cost earmarked for drugs in the corresponding Diagnosis-Related Groups cost currently applied in France.

Patient Transport Costs. The number of journeys to hospital was derived from the number of hospitalizations and consultations. An economic study conducted in 33 patients showed that the mean distance between home and hospital was about 25 km. We took into account the French National Health Service reimbursement price [18].

Statistical Methods

EFS and OS were estimated by the Kaplan-Meier method. Each group was compared to the control group (HD-LV5FU2 protocol) by the log-rank test. Costs were compared by using a nonparametric test (Wilcoxon test) because costs were not normally distributed. If the EFS of a regimen was statistically different of the EFS from the HD-LV5FU2 group, an incremental cost-effectiveness ratio (ICER) was calculated as the ratio of the difference in costs to the difference in effects between the two regimens. The ICER confidence interval was estimated by using the bootstrap method, which consisted in a resampling procedure with replacement based on the generation of 1,000 replications of the ratio. All tests were two-sided.

Sensitivity Analysis

Sensitivity analyses were performed to test the robustness of the results in relation to changes in the major unit costs. Sensitivity analyses were based on the minimum and maximum values of hospitalization costs, drug acquisition prices and on various hypotheses concerning the price of patient transport. In a bivariate sensitivity analysis, the more unfavorable scenario for raltitrexed, which consists of considering maximum values of chemotherapy costs and minimal values of hospitalization costs, was assessed (scenario 1). Two scenarios consisted to increase the raltitrexed acquisition cost or/and to decrease the cost of hospital stay in order to that the total cost per patient treated by raltitrexed would become superior to the total cost of patient treated by HD-LV5FU2 (scenarios 2–4).

Results

Between March 1997 and March 2001, 294 patients were randomized in 39 centers: 74 in the HD-LV5FU2 arm, 75 in the LD-LV5FU2 arm, 73 in the weekly 5FU arm and 72 in the raltitrexed arm. 65% were males. The median age was 64.3 years (range 29–83), with 77 (26%) patients over the age of 70 years. The site of the primary cancer was the colon in 226 (77%) patients. 37 patients (12%) had previously received adjuvant chemotherapy.

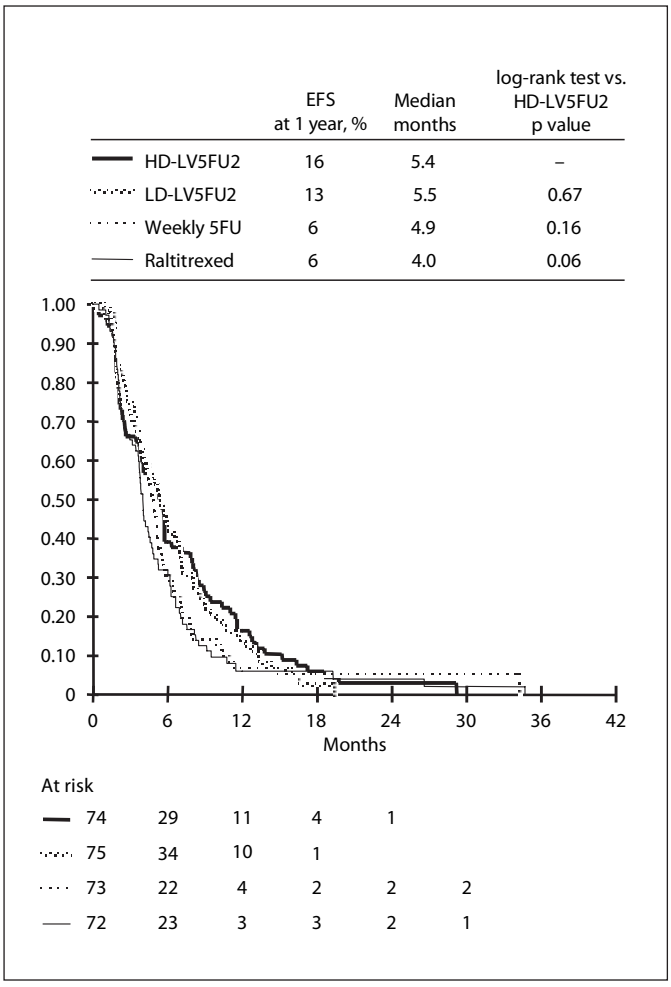

Fig. 1. Event-free survival (EFS).

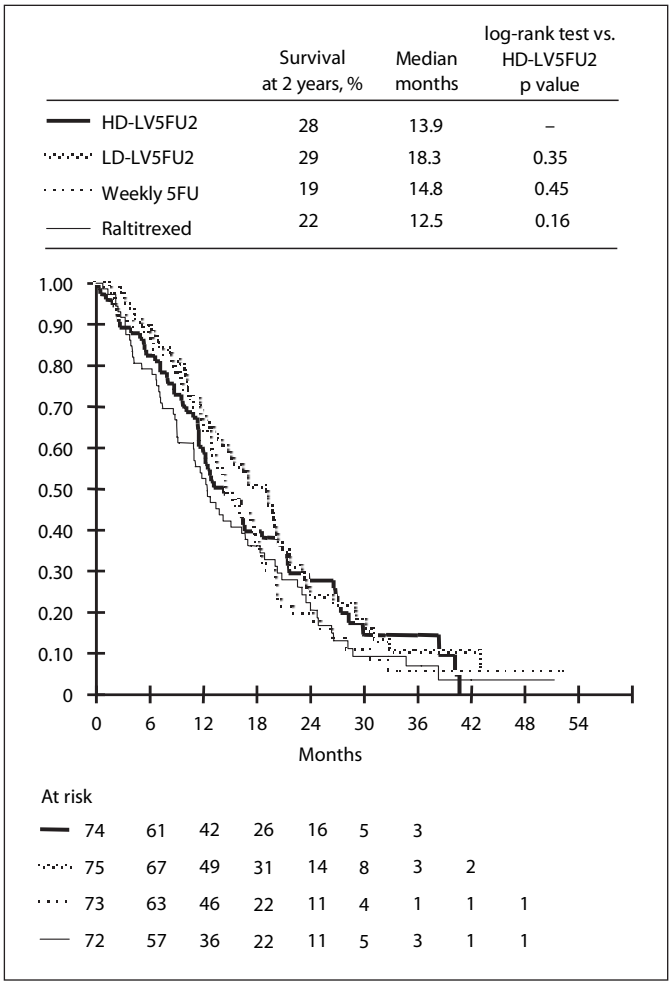

Fig. 2. Overall survival (OS).

The four groups were comparable with respect to baseline demographic and disease characteristics.

Disease progression occurred in 1 patient allocated to the HD-LV5FU2 arm before treatment. Costs have not been reported for this patient. The economic study was therefore based on 293 patients.

The median duration of follow-up was 32.5 months (range 30.0–36.7), with no significant difference between the four groups. EFS and OS are presented in figures 1 and 2. The median EFS was 5.4 months in the HD-LV5FU2 arm, 5.5 months in the LD-LV5FU2 arm, 4.9 months for weekly 5FU, and 4.0 months for raltitrexed. EFS was shorter in the raltitrexed arm than for HD-LV5FU2 ($p = 0.055$). EFS in the others two arms was not significantly different from that in the HD-LV5FU2 arm. There was no significant difference in the median OS for all randomized patients.

The total number of cycles ranged from 1 to 29. The mean number of treatment cycles was 6 in the HD-LV5FU2, LD-LV5FU2 and raltitrexed arms, and 3 in the weekly 5FU arm. The median duration of chemotherapy was comparable between HD-LV5FU2 (23.1 weeks, from 0.3 to 89.6) and LD-LV5FU2 (21.1 weeks, from 2.1 to 73.1, $p = 0.48$), and weekly 5FU (18.9 weeks, from 0.1 to 67.2, $p = 0.14$), but was shorter in the raltitrexed arm (16.1 weeks, from 0.1 to 87.1, $p = 0.02$).

Hospitalizations for chemotherapy administration are described in table 2. There were fewer hospital visits and shorter hospital stays in the raltitrexed arm because of the administration schedule. The management of patients treated with raltitrexed was also different from that of the other three groups treated with 5FU: hospitalizations were more often in the hospital day ward and hardly ever in the outpatient clinic.

Table 2. Hospitalizations for chemotherapy: number of visits and duration of stay

	HD-LV5FU2 n = 73	LD-LV5FU2 n = 75	Weekly 5FU n = 73	Raltitrexed n = 72
Hospitalization in a conventional ward				
Patients	47	45	44	28
Hospitalizations	386	469	524	152
Hospital day ward				
Patients	39	38	36	51
Hospitalizations	995	761	547	280
Outpatient clinic (hospital at home)				
Patients	18	16	16	2
Hospitalizations	250	310	309	14
Overall duration of stay by patient, days				
Mean (SD)	30.1 (23.2)	28.2 (17.0)	23.9 (16.8)	6.6 (5.4)
Range	3–106	8–115	1–79	1–35
Compared to HD-LV5FU2		p = 0.50	p = 0.054	p < 0.0001

Table 3. Toxicity

	HD-LV5FU2	LD-LV5FU2	Weekly 5FU	Raltitrexed
Treatment-related deaths	0	0	0	2
Patients with at least one episode of grade 3-4 toxicity Compared to HD-LV5FU2	19 (26%)	19 (25%) p = 0.92	28 (38%) p = 0.11	34 (47%) p = 0.008
At least one episode of grade 3-4 toxicity per cycle	23 (5%)	23 (5%)	37 (8%)	51 (12%)
Patients with at least one hospitalization for toxicity Compared to HD-LV5FU2	10 (13.5%)	11 (14.7%) p = 0.87	17 (23.3%) p = 0.14	19 (26.4%) p = 0.056
Number of hospitalizations for toxicity[1]	10	20	26	29
Duration of hospitalization by patient, days Compared to HD-LV5FU2	0.8 ± 2.5	1.6 ± 6.3 p = 0.31	2.2 ± 6.2 p = 0.07	3.5 ± 9.3 p = 0.02

[1] There were 54 hospitalizations in a conventional ward, 14 hospitalizations in the hospital day ward, 9 hospitalizations in the surgical unit, and 8 hospitalizations in the ICU for the management of toxicities.

The toxicity is presented in table 3. Raltitrexed was more toxic than HD-LV5FU2: 2 treatment-related deaths occurred in this arm and the percentage of patients which experienced at least one episode of grade 3–4 toxicity was higher than in the HD-LV5FU2 arm (p = 0.008). Weekly 5FU was slightly more toxic than HD-LV5FU2, but the difference did not reach statistical significance. There was no significant difference in toxicity between LD-LV5FU2 as compared to HD-LV5FU2.

The number of patients requiring at least one hospitalization and the number of hospitalizations for toxicity were higher in the raltitrexed arm compared to the HD-LV5FU2 arm (p = 0.006). They were also higher in the weekly 5FU arm than in the HD-LV5FU2 arm but the difference was not statistically significant.

The duration of other hospitalizations related to cancer complications (surgery, palliative care, and other treatment modalities such as radiofrequency ablation) were comparable in the four groups: 1.9 days in the two LV5FU2 arms, 2.0 for weekly 5FU, and 1.5 in the raltitrexed arm.

Table 4. Cost (mean ± SD), [range]) in Euros

	HD-LV5FU2	% of total cost	LD-LV5FU2	% of total cost	Weekly 5FU	% of total cost	Raltitrexed	% of total cost
Administration of chemotherapy								
Hospitalizations	11,512 (10,123) [888–44,701]	72.2	10,583 (7,429) [888–47,230]	71.1	8,656 (6,896) [496–33,012]	62.9	2,746 (2,557) [456–17,190]	25.7
Chemotherapy and other drugs	493 (370) [27–1,737]	3.1	139 (83) [23–396]	0.9	155 (108) [7–584]	1.1	3,632 (2,380) [408–13,448]	34.0
Travel	1,026 (1,021) [0–5,170]	6.4	946 (699) [0–3,090]	6.4	1,172 (2,674) [0–22,760]	8.5	346 (266) [0–1,664]	3.2
Total chemotherapy	13,061 (11,242) [1,097–51,053]	81.7	11,668 (7,850) [931–48,754]	78.4	9,983 (7,789) [563–35,486]	72.5	6,659 (4,814) [920–28,228]	62.9
Management of toxicity								
Hospitalizations	370 (1,168) [0–6,783]	2.3	848 (3,020) [0–18,892]	5.7	1,170 (3,346) [0–23,380]	8.5	1,788 (4,983) [0–34,976]	16.7
Drugs	77 (176) [0–898]	0.5	60 (123) [0–540]	0.4	158 (664) [0–5,597]	1.2	98 (199) [0–1,145]	0.9
Travel	100 (176) [0–965]	0.6	111 (256) [0–1,737]	0.7	158 (237) [0–965]	1.2	166 (257) [0–1,351]	1.6
Total toxicity	547 (1,337) [0–7,239]	3.4	1,019 (3,192) [0–19,731]	6.8	1,487 (3,932) [0–25,166]	10.9	2,079 (5,279) [0–36,383]	19.2
Treatment for cancer complications								
Hospitalizations	929 (2,829) [0–19,985]	5.9	848 (3,020) [0–18,892]	5.8	901 (3,000) [0–19,070]	6.6	684 (2,154) [0–11,499]	6.4
Follow-up								
Follow-up	1,433 (769) [577–3,731]	9.0	1,343 (562) [555–3,251]	9.0	1,388 (603) [566–3,619]	10.0	1,227 (603) [566–4,509]	11.5
Total	15,970 (12,522) [1,793–63,478]	100	14,888 (9,133) [1,606–51,887]	100	13,760 (10,828) [1,129–49,764]	100	10,687 (7,353) [1,882–39,193]	100

Costs

Costs are presented in table 4: mean total costs were not significantly different between HD-LV5FU2 (€ 15,970), LD-LV5FU2 (€ 14,888, p = 0.79), or weekly 5FU (€ 13,760, p = 0.28). Treatment in the raltitrexed arm (€ 10,687) was significantly less expensive (p = 0.008) than in the HD-LV5FU2.

Hospitalizations for chemotherapy administration represented about 70% of total costs in the two LV5FU2 arms, 63% in the weekly infusion FU arm, and only 26% in the raltitrexed arm. The cost of chemotherapy was very low, less than 3% of the total costs in the three arms with 5FU, whereas raltitrexed acquisition represented 34% of total costs. Cost induced by toxicity was 3% in HD-LV5FU2 arm, 7% in LD-LV5FU2 arm, 11% in weekly infusion FU arm, and 19% in the raltitrexed arm (table 4).

As the EFS in the LD-LV5FU2 and weekly 5FU arms were not significantly different from that in the HD-LV5FU2 arm, the corresponding cost-effectiveness ratios were not calculated. The ICER of the HD-LV5FU2 as compared to the raltitrexed was € 45,956 (95% CI = € –211,645 to +338,701). It represented the additional cost that we have to pay per year of EFS gained with HD-LV5FU2 as compared to raltitrexed.

Sensitivity analyses were based on the minimum and maximum values of hospitalization costs, drug acquisition prices and on various hypotheses concerning the price of patient transport. In a univariate sensitivity analysis, none of them modified the conclusion of the analysis. In a bivariate sensitivity analysis, the more unfavorable scenario for raltitrexed, which consists of considering maximum values of chemotherapy costs and minimal values of hospitalization costs, does not change the initial conclusion (scenario 1). The total cost per patient treated by raltitrexed would become superior to the total cost of patients treated by HD-LV5FU2 if the raltitrexed unit cost were multiplied by 2.5 (scenario 2). The four strategies compared would lead to similar costs if the cost of hospital stays were reduced to € 152 per day (scenario 3), or if the raltitrexed unit cost were multiplied by 1.5 and the cost of hospital stays were reduced to € 229 per day (scenario 4, table 5). The conclusions of the main analysis are then robust, as these hypotheses appear unrealistic in practice.

Table 5. Total cost per patient according various hypotheses (Euros)

	Scenario 1	Scenario 2	Scenario 3	Scenario 4
HD-LV5FU2	14,017 ± 10,300	15,971 ± 12,529	7,971 ± 5,527	10,202 ± 7,290
LD-LV5FU2	13,010 ± 7,517	14,887 ± 9,132	7,255 ± 3,617	9,354 ± 4,991
Weekly 5FU	12,198 ± 9,247	13,760 ± 10,828	7,146 ± 5,194	8,968 ± 6,541
Raltitrexed	9,852 ± 6,093	16,135 ± 9,873	7,231 ± 4,137	8,101 ± 4,762

Description of the sensitivity analyses performed: Scenario 1: minimum values of hospitalization and maximum value of chemotherapy acquisition cost; Scenario 2: raltitrexed acquisition cost multiplied by 2.5; Scenario 3: cost of hospital stay fixed at € 152; Scenario 4: raltitrexed acquisition cost multiplied by 1.5 and cost of hospital stay fixed at € 229.

Discussion

Neither of the two protocols based on 5FU (LD-LV5FU2 and weekly 5FU infusion) significantly improved EFS and OS, as compared to HD-LV5FU2 in patients with advanced colorectal cancer. In terms of toxicity, the two LV5FU2 regimens were not different and the weekly 5FU regimen induced more toxicity than the LV5FU2 regimens. Raltitrexed was associated with a shorter EFS and more toxic events compared to HD-LV5FU2. This result is in agreement with the literature [13, 19–21].

As raltitrexed is less active and more toxic than HD-LV5FU2, its use will be restricted to patients in whom the use of fluoropyrimidines is strongly contraindicated [22]. However, it is noteworthy that the total cost per patient was significantly lower in the raltitrexed arm than in the HD-LV5FU2 arm because the very high cost for raltitrexed acquisition was offset by fewer and shorter hospitalizations for chemotherapy administration due to the timing of the infusion (1 day every 3 weeks, instead of 2 days every 2 weeks). It could partly be related to a reduced total duration of chemotherapy (whether due to lower efficacy and increased toxicity). In addition, patients in the raltitrexed arm were hospitalized more frequently in a hospital day ward. Today, the total cost per patient in the LV5FU2 group would probably be lower than the cost calculated in this study, due to a reduction in the duration of hospitalization with this protocol. Hospitalizations for toxicities were more numerous and longer in the raltitrexed arm than in the HD-LV5FU2 arm. The management of toxicities, including hospitalizations, drugs and patient transport represents almost 20% of the total cost per patient in the raltitrexed arm, versus less than 10% in the other three arms. Sensibility analyses showed that this difference in cost in favor of raltitrexed was robust. The total cost per patient was similar for the three treatments with 5FU in which the greatest cost component was hospitalization (about 75%), the cost for drug acquisition being negligible in these groups.

Chemotherapy for metastatic colorectal cancer has changed during the last decade. At present, in Europe and in the USA, the mostly used regimens for metastatic disease contain irinotecan or oxaliplatin in combination with 5FU or capecitabine [23–25]. They showed an increased response rate, progression-free survival with both drugs, and OS, only with the irinotecan-based regimen. Moreover, after aggressive first-line chemotherapy, some patients can undergo surgical resection of the metastases, initially considered as unresectable. We still do not know if these aggressive first-line therapies (irinotecan and oxaliplatin) should be proposed to all metastatic patients or whether they should be reserved exclusively for second-line treatment [26]. Two large multicenter trials, in Great Britain and France, are addressing this question and hopefully answers will be provided in approximately 2 years. New aggressive protocols combining raltitrexed with oxaliplatin or irinotecan are currently evaluated in phase II studies, either in first- or second-line treatment of metastatic colorectal cancer [27–30].

The preliminary economic study based on the 33 first patients included in the Gustave-Roussy Institute showed that the total cost per patient was significantly higher in the raltitrexed group than in LV5FU2 group [31]. This higher cost was related to a very high rate of severe toxicity in the 8 patients treated with raltitrexed: 9 hospitalizations, including one in the intensive care unit for 30 days. Costs based on these 8 patients were overestimated in the raltitrexed arm. A better estimation of the costs is possible if all the randomized patients are included in the economic study.

Two economic studies based on the randomized trial reported by Cunningham et al. [6] comparing raltitrexed with 5FU in the Mayo regimen have been published. The

first study performed by Groener et al. [14] used Dutch estimates of unit costs and took into account direct medical costs (hospitalizations, drugs, follow-up and travel costs). The second economic study using the same clinical data was conducted by Kerr and O'Connor [12] in the UK and excluded travel costs. The total costs per patient were similar for the two treatment arms in the two studies. Two other economic studies compared raltitrexed to the LV5FU2 regimen. The study by Ross et al. [11] is based on a retrospective analysis of 116 patients at the Royal Marsden Hospital for whom data were complete. It included direct medical costs (hospitalizations, chemotherapy, follow-up and outpatient visits) of four regimens (Mayo, LV5FU2, Lokich and raltitrexed). The mean monthly treatment costs were € 1,411, 3,001, 1,786, and 1,859 respectively. These results should be interpreted with caution because patients were not randomized and the comparability of the baseline characteristics of the patients was unknown. Patients were selected on the basis of complete patient notes. The study by Hale et al. [13] was undertaken on a subsample of a randomized trial which compared LV5FU2, Lokich (continuously infused fluorouracil) and raltitrexed regimens. The economic study was based on patients from 6 of the 45 centers and took into account direct and indirect costs. Total costs per 12 weeks of treatment were respectively € 7,470, 3,810, and 3,869 for LV5FU2, Lokich and raltitrexed regimens. In these two studies, the LV5FU2 regimen was significantly more expensive than the other regimens.

Economic outcomes measured in association with clinical trials are often considered of secondary importance as there are no a priori hypotheses, the sample size is small and data are frequently missing. Even when properly designed and conducted, the external validity of economic analyses with clinical trials may be low, this being related to a lack of representativeness and limited generalizability due to strict eligibility criteria [32]. The trial population may be associated with resource utilization and costs that differ considerably from that of routine practice and early clinical trial costs may not be representative of what they would really be with more experience [33]. This is probably not a major drawback of our study because the trial evaluated four regimens currently used in clinical practice and patients were treated in several hospitals including research centers (university hospitals and cancer centers) but also general hospitals and private hospitals (respectively 21.5, 36.4, 33.3, 8.8% of the patient study population). This suggests that the external validity of the results may also be good and therefore could be extrapolated to general practice.

Conclusion

The lower efficacy and the higher toxicity observed with raltitrexed make it a clinically inferior regimen despite its ease of administration and the lower costs of this regimen. The HD-LV5FU2 protocol remains a better treatment for metastatic colorectal cancer. There is no advantage to using the weekly 5FU regimen in terms of efficacy, toxicity or cost. The LD-LV5FU2 regimen could be a good alternative, because the cost of chemotherapy acquisition is reduced without compromising its efficacy.

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