Anti-Cancer Drugs 1999, **10**, pp. 283–288

Clinical study

An economic evaluation of Tomudex (raltitrexed) and 5-fluorouracil plus leucovorin in advanced colorectal cancer

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Our objective was to establish the balance between costs and effects of treatment with Tomudex (raltitrexed) as an alternative to treatment with 5-fluorouracil (5-FU) plus leucovorin (LV) in patients with advanced colorectal cancer. Data were used from an international, open label randomized clinical trial. Costs were calculated by multiplying resource utilization data with Dutch estimates of unit costs. Effects have been expressed in terms of 6 months and 1 year survival, and in terms of the number of patients without severe adverse events including WHO grade 3 and 4 leucopenia, mucositis, anemia and severe asthenia. Cost effectiveness is expressed in terms of costs per additional day of survival and costs per additional patient without any severe adverse event. The clinical results did not show significant survival differences implying great uncertainty about the cost-effectiveness of raltitrexed in terms of additional costs per additional life-year gained. However, 80% of the initially higher cost of raltitrexed ($3132 per patient) is compensated by savings due to a more convenient administration scheme leading to a net cost of $626 per patient treated. Weighed against the decrease in adverse events, a cost–effectiveness ratio results of $3936 per additional patient free of any severe adverse event. More favorable estimates result when the convenience of the administration scheme is valued in positive monetary terms.

Key words: Advanced colorectal cancer, chemotherapy, economic evaluation, palliation, thymidylate synthase inhibitor, Tomudex.

Introduction

In 1992 about 1600 patients were diagnosed with advanced colorectal cancer in The Netherlands.[1] About 15% of these patients received chemotherapy to control the disseminated disease, palliate the symptoms of the disease and extend survival.[2]

The standard chemotherapeutic treatment for colorectal cancer consists of leucovorin (LV)-modulated 5-fluorouracil (5-FU) schedules. In many countries the Mayo regimen (425 mg/m^2 5-FU and 20 mg/m^2 LV for 5 days every 4–5 weeks) is considered as the standard treatment. This regimen has been shown to offer statistically significant survival advantages over 5-FU alone[3] and to be at least comparable to regimens using higher doses of LV.[4] The Mayo regimen is administered during five consecutive days and repeated at week 4, week 8 and every 5 weeks thereafter. Recently a new cytostatic agent was introduced (Tomudex, raltitrexed; Zeneca Pharmaceuticals, Macclesfield, UK). Raltitrexed is administered as an i.v. infusion at a dose of 3 mg/m^2 once every 3 weeks.

In a multinational randomized clinical trial (n=439), the clinical efficacy of raltitrexed (n=223) was compared to that of the Mayo regimen of 5-FU + LV (n=216).[5,6] The results showed no statistically significant differences in tumor response rate and survival. However, in terms of the tolerability profile advantages were shown in favor of raltitrexed. Patients treated with raltitrexed spent a substantially shorter time in hospital for dosing and had statistically significant lower rates of WHO grade 3 and 4 leucopenia and mucositis. On the other hand, raltitrexed was associated with a slightly higher incidence of WHO grade 3 and 4 anemia, and a non-significant trend towards a higher incidence of severe asthenia.

Tomudex is a trademark, the property of Zeneca Ltd. The authors would like to thank Zeneca Farma, Ridderkerk, The Netherlands for their sponsorship of this study.

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Although the data indicate that raltitrexed is as effective as the standard therapy, and offers more ease of administration and a better tolerability profile, it should be realized, in this era of cost containment in health care, that safety, efficacy and tolerability are not the only arguments anymore in decision making about the best alternative treatment. Increasingly the question is asked about the balance between costs and effects. This question is addressed for the case of The Netherlands. For this purpose, the data about resource utilization—gathered alongside the trial—have been multiplied with Dutch estimates of unit costs. The difference in costs is put in perspective with the differences in effects, (i) measured in terms of differences in survival, (ii) with the difference in effects measured in terms of differences in tolerability and (iii) with its difference in administration.

Methods

Data were obtained from an open randomized clinical study including 439 patients. Data on resource use and effects were available from 220 patients treated with raltitrexed and 212 patients treated with 5-FU + LV. The average duration of treatment was 20.2 weeks for raltitrexed and 20.7 weeks for 5-FU + LV. Patients treated with raltitrexed went on average through 6.3 cycles of 3.2 weeks. Patients treated with 5-FU + LV went on average through 4.6 cycles of 4.6 weeks. The median survival was 10.1 and 10.2 months for patients treated with raltitrexed and 5-FU + LV, respectively.

Costs

During the phase III study (n=439) data were collected on resource utilization. Costs were calculated per patient by multiplying the volumes per patient with estimates of unit costs from The Netherlands. Cost estimates were presented broken down in costs that are directly related to the treatment regimens and costs that are indirectly related to the treatment regimen. Among the first are the costs of the drugs themselves and all costs that are related to the administration of the drugs, including the costs of hematology and biochemistry tests, and the transport costs from home to hospital associated with the drug regimen. The non-drug treatment-related costs concern all other costs, including transport costs for those variables. The non-drug treatment-related costs were considered to have a rather random character that is related to the underlying disease, and to the effectiveness and to the side effects of the treatments. The following costs were considered:

Drug-regimen related costs:

- drugs and preparation;
- drug administration at the outpatient 'day case' department;
- diagnostics related to treatment (laboratory tests);
- transport from and to hospital.

Non-drug-regimen related costs:

- hospitalizations (at the oncology ward and intensive care unit);
- treatment of chemotherapy related side effects;
- non-treatment related diagnostics [including computed tomography (CT) scans, X-rays];
- hospital outpatient visits;
- General Practitioner (GP) visits;
- transport from and to hospital.

All volumes of resource utilization were collected alongside the trial except the volumes related to transport and laboratory tests. The number of visits from and to hospital have been derived from the data about drug administration, and from the data about hospitalizations, out-patient visits, laboratory tests and other tests. The number of laboratory tests has been derived from the administration schedules, taking account of the number of visits and the number of cycles. Indirect medical costs were not considered as there is no survival benefit and indirect costs due to loss of productivity of paid labor were considered to be very small.

The unit costs of 'day case days', hospitalization, laboratory tests and outpatient visits were derived from studies performed by the Institute for Medical Technology Assessment.[7,8] Drug costs (including cytostatics and co-medication) were taken from the Dutch pharmaceutical price list.[9] The drug costs of 5-FU and LV reflect generic prices. Costs of preparation of drugs (of both 5-FU + LV and raltitrexed) were based on additional research among hospital pharmacists. Costs of CT scans, X-rays and GP visits reflect charges.[10] Estimates of the costs of transport were taken from literature.[11] Costs are expressed in US$ using an exchange rate of Dfl 1.93=US$1.

Additionally, the relationship between the costs per patient and the occurrence of side effects was analyzed using a linear regression analysis with the costs per patient as the dependent variable. The explanatory variables are the use of raltitrexed, the duration of follow-up, and the occurrence of mucositis, leucopenia, anemia and asthenia. The constant term—as estimated in the regression equation—is interpreted as the total costs not associated with the duration of follow-up for the occurrence of side effects. The parameter associated with the duration

of follow-up measures the additional costs per day, correcting for differences in follow-up. The parameters connected to the occurrence of an adverse event were interpreted as the additional costs associated with patients confronted with such an adverse event. It is noted that these costs may not only include the direct costs of treating the adverse events but also the indirect costs related to such events. The parameter associated with the use of raltitrexed measures the net costs of raltitrexed disregarding its effects on side effects.

Effects

Effects have (i) been expressed in terms of survival and (ii) in terms of the additional percentage of patients without any of the following severe adverse events: leucopenia, mucositis, anemia (all WHO grade 3 and 4) or any episodes of severe asthenia. The latter variable was not defined as an effectiveness measure before the trial started. However, various studies have shown that the main additional effects of raltitrexed—next to its more convenient dosing schedule—lie in the side effect profile.[12,13] Therefore it seems appropriate—as part of the economic evaluation—to put the difference in costs in perspective of the difference in the side effect profile.

Cost effectiveness

Primarily, the balance between costs and effects has been expressed in terms of the additional costs per additional survivor after 6 and 12 months. Secondarily, cost effectiveness has been expressed as the additional costs per additional patient without WHO grade 3 and 4 leucopenia and mucositis, anemia and asthenia.

Statistical methods

For statistical comparisons between the two treatment groups the Wilcoxon rank-sum test was used in the case of non-normally distributed continuous variables

Table 1. Resource utilization (total count), unit costs and costs (per patient)

	Volumes (total count)		Unit costs	Costs (per patient)		*p*
	Raltitrexed	5-FU+LV	($)	Raltitrexed ($)	5-FU+LV ($)	
Regimen-related components						
medication						
raltitrexed (vials)	4071		170.78	3132		
5-FU (g)		3202.93	7.88		119	
LV (g)		166.94	701.40		552	
drug administration						
raltitrexed (injections)	1391		9.68	61		
5-FU (injections)		4785	9.97		225	
LV (injections)		4785	9.38		212	
day case (days)	870.5	2748.5	168.91	662	2190	
travel (trips)	1487	4647	6.71	45	147	
scheduled follow-up test						
hematology (tests)	4394	5459	4.82	95	124	
biochemistry (tests)	1391	957	29.84	187	135	
travel (trips)	3003	3501	6.71	91	111	
sub-total				4273	3815	
Non-regimen-related components						
side effects	–	–	–	43	30	
ICU days	11	38	1255.96	62	225	0.504
ward days	1187.5	857.5	270.98	1450	1096	0.078
outpatient visits	214	257	41.19	40	50	0.997
GP visits	85	172	23.32	9	19	0.522
CT scans	287	296	150.26	194	210	
X-rays	10	9	25.03	1	1	
travel costs (trips)	656	656	6.71	20	21	
sub-total				1819	1651	
Grand total				6092	5466	

and for categorical variables the χ^2 test was applied. Differences were considered to be statistically significant if $p < 0.05$.

Cost effectiveness is addressed by central estimates surrounded with 95% confidence intervals. The central estimates concern the increase in the average costs per patient divided by the increase in expected effectiveness per patient. The confidence intervals were calculated by Fieller's method.[14] Probability ellipses were estimated following the methodology as described by Van Hout *et al.*[15]

Results

Table 1 shows the results from the calculation in which all units of resource utilization were multiplied with Dutch estimates of unit costs including only p values for those variables with a random character. It was concluded that of the additional costs due to the drug costs of raltitrexed, 80% is compensated by a decrease in the costs of drug preparation, day case days, and the costs of traveling to and from hospital, taking account of a slight increase in the costs of laboratory tests. All other costs did not reach statistically significance.

According to the results in Table 1, the costs of side effects were only a fraction of the total costs. However, these costs only included those items that could directly be linked to the treatment of adverse events. Table 2 represents the results in a slightly different way, using the results from the linear regression analysis. The fixed costs per patient were estimated at \$2980 and the additional costs per day at \$5.83 (p=0.0000). The respective additional costs associated with patients who had at least one episode of mucositis, leucopenia anemia and asthenia were estimated at, respectively, \$531 for mucositis (p=0.1522), \$1427 (p=0.0002) for leucopenia, \$2328 (p=0.0004) for anemia and \$758 (p=0.1797) for an episode of severe asthenia. The net costs for treatment of patients with raltitrexed—disregarding the differences in side effect profile but including the difference in administration schedule—were estimated at \$723 (p=0.0167) per patient.

Table 3 summarizes the trial results in terms of effectiveness and cost effectiveness. When addressing survival, no significant differences were found, and as

Table 2. Costs per patient in relationship to side effects

	Per cent of resource use		Unit costs	Costs (per patient)	
	Raltitrexed	5-FU+LV	($)	Raltitrexed ($)	5-FU+LV ($)
Fixed costs	100.00%	100.00%	2980	2980	2980
Raltitrexed	100.00%	0.00%	723	723	0
Follow-up	322 days	317 days	6	1912	1880
Mucositis	3.15%	21.23%	531	17	113
Leucopenia	14.41%	29.72%	1427	206	424
Anemia	9.01%	2.36%	2328	210	55
Asthenia	5.86%	1.89%	758	44	14
Total				6092	5466

Table 3. Costs, effects and cost–effectiveness ratios of raltitrexed versus 5-FU+LV

	Raltitrexed	5-FU+LV	Difference	p^a
Costs per patient ($)	6092	5466	626	0.0332
Survival after 6 months (%)	72.07	67.92	4.15	0.8277
One-year survival (%)	44.14	43.87	0.28	0.5232
Free of mucositis, leucopenia, anemia and asthenia (%)	72.97	57.08	15.90	1.0000

Cost-effectiveness ratio's	Lower 95% limit	Central estimate	Upper 95% limit
Costs per additional 6 months survivor ($)	−infinity	\$15086	+infinity
Costs per additional 1 year survivor (%)	−infinity	\$154611	+infinity
Costs per additional patient free of mucositis, leucopenia, anemia and asthenia (%)	−\$297	\$3936	\$10560

[a]Here, the p values indicate the probability that the results differ in favor of raltitrexed.

a consequence the upper and lower 95% limits of the cost effectiveness (with survival in the denominator, potentially equal to zero) were estimated at plus and minus infinity. The cost per additional patient without severe adverse events showed significant differences and the upper (one-sided) 95% limit was estimated at $8920. Figure 1 illustrates the estimate and its uncertainties. Costs and effects are depicted as a bivariate normal distribution and the outer ellipse—which should be interpreted as a two-dimensional confidence interval—defines the smallest area where both costs and effects are located with a probability of 95%.[15]

The results in terms of costs are mainly driven by the unit costs of the drugs considered and the costs of administering the drugs. The costs of day case days were verified with previously estimated data.[7,8] No account was taken of the value that may be attained to the time that the patients and their family spend for traveling and for their time at the hospital. It was estimated that when this time would be valued at, at least $43 per visit, there are cost savings for the raltitrexed treatment.

Discussion

Currently, raltitrexed is registered for palliative treatment in patients with Duke's D colorectal cancer. In terms of tumor response and survival, it has been shown to be as effective as the standard therapy. Additionally, it has been shown to cause significantly less WHO grade 3 and 4 mucositis and leucopenia compared to the standard treatment. On the other hand, raltitrexed was associated with higher incidence of anemia and a non-significant trend towards a higher incidence of asthenia. In general, the advantages seem to outweigh the potential negative side effects. The randomized clinical trial also collected data on quality of life. In this study no significant differences in quality of life were found, which might be due to the fact that in the heterogeneous population such a difference is extremely difficult to confirm in a statistically valid way.

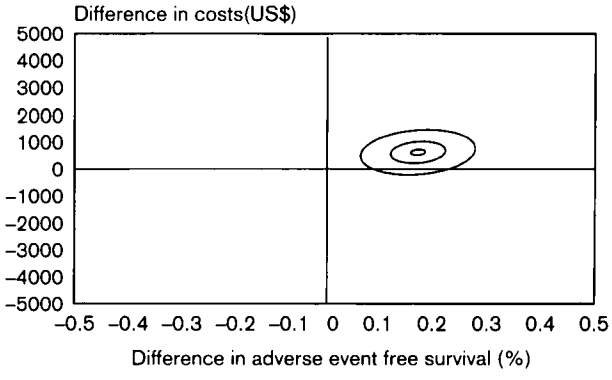

Figure 1. Costs and effects in terms of patients without either mucositis or leucopenia comparing raltitrexed treatment versus the 5-FU + LV treatment. The outer ellipse defines the smallest area where both costs and effect are located with 95% probability. The middle ellipse corresponds with a probability of 50% and the inner ellipse with a probability of 5%.

The analysis presented combines data from a randomized clinical trial with Dutch unit costs. There are at least two potential major drawbacks of the method used. First, the trial only included nine patients from The Netherlands and it is questionable whether it is legitimate to use the data from all countries to estimate costs for The Netherlands. For this reason a test for homogeneity for ward days, outpatient visits and GP visits was performed which confirmed the method was valid. Additionally, these items only make up a small proportion of the final balance. They do not differ significantly, and the bottom line differences only concern the costs of the drug and the costs of administration. So, with respect to the largest cost components, there was no heterogeneity, and without major differences in the costs of medication and the costs associated with the administration, the conclusions can be generalized to other countries. Moreover, in the case of major differences, the analysis is easily adapted to other countries by using local cost figures in Table 1 and by recalculating the costs per patient. The second potential drawback from using data from a trial is that these data may not be representative for daily practice. This holds especially for the raltitrexed treatment, because it is not known how it may change in daily clinical practice. Physicians confronted with a new cytotoxic agent are usually risk averse and may use it cautiously rather than efficiently. The fact that treatments change, once established, is also shown by a survey in which physicians stated that, due to lack of experience with raltitrexed, laboratory tests were performed more often than in the standard chemotherapy treatment.

Although 5-FU regimens using higher doses of LV proved to have no superiority over the Mayo regimen,[4] a survey among Dutch oncologists proved that patients with advanced colorectal cancer are often treated with regimens using higher doses of LV: the so-called Bologna regimen (600 mg/m^2 5-FU + 200 mg/m^2 LV once a week) and a weekly bolus schedule (425 mg/m^2 5-FU + 80 mg/m^2 LV once a week). This would increase the costs of the 5-FU + LV treatment by

approximately $4361 and $1363, respectively. Therefore, the treatment with raltitrexed can be positioned—in terms of the costs of treatment—between the Mayo regimen and this weekly bolus schedule of 5-FU + LV. We conclude that there is a definite need for additional research about the balance between the costs and the effects of such a weekly bolus schedule of 5-FU + LV, not only in comparison to the Mayo regimen, but also in comparison to raltitrexed.

Without reliable data on quality of life, the balance between the additional costs and effects of raltitrexed versus 5-FU + LV is probably best assessed by a multicriteria analysis. On the one hand, there are the additional costs due to raltitrexed, approximately $626 per patient and an approximate 2.5% increase in the need for blood transfusions. On the other hand, raltitrexed comprises a more convenient dosing schedule implying that patients treated with raltitrexed spend less time at the outpatient 'day case' department, and travel less often to hospital for drug administration and thus are less often away from normal activities than patients treated with 5-FU + LV. In a pilot study, 45 patients with advanced colorectal cancer were shown 'blinded' descriptions of four different chemotherapy regimens (three 5-FU-based regimens and the raltitrexed treatment) and asked to select which they most and least preferred assuming equal efficacy and safety. It appeared that the raltitrexed treatment was preferred by 87% of patients, generally because of its more convenient dosing schedule.[16] In addition, the raltitrexed treatment offers a 23% decrease of the incidence of WHO grade 3 and 4 mucositis and leucopenia. Such advantages may be extremely important when considering treatment for patients with a limited life expectancy.

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(Received 29 October 1998; revised form accepted 30 November 1998)