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Original Paper

'Tomudex' (ZD1694): Results of a Randomised Trial in Advanced Colorectal Cancer Demonstrate Efficacy and Reduced Mucositis and Leucopenia

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'Tomudex' (ZD1694), a direct and specific thymidylate synthase (TS) inhibitor entered phase III studies in November 1993. We present here the first analysis of a randomised multicentre, international phase III study. 439 patients with previously untreated advanced colorectal cancer were randomised to Tomudex 3.0 mg/m^2 given once every 3 weeks or 5-fluorouracil (5-FU) 425 mg/m^2 and leucovorin (LV) 20 mg/m^2 for 5 days (the Mayo regimen), given every 4–5 weeks. Patients were evaluated weekly for toxicity and every 12 weeks for objective response. The two groups were well matched in terms of demographic characteristics. The mean age of the patients was 61 years and most had either liver (78%) or lung (25–29%) metastases. Ninety seven per cent of patients allocated to Tomudex and 94% of those allocated to 5-FU plus LV had measurable disease. Response was assessed using WHO/UICC criteria; all response data were source validated; 19.8% of patients who received Tomudex and 12.7% of patients who received 5-FU plus LV had complete or partial responses ($P = 0.059$, odds ratio 1.7, 95% confidence limits 0.98–2.81). There were no statistically significant differences in time to progression or survival between the two groups. Patients who received Tomudex spent a substantially shorter time in hospital for dosing and had significantly lower rates of grade 3 and 4 toxicities such as leucopenia and mucositis. Patients who received Tomudex had a significantly higher incidence of reversible grade 3 or 4 increase in transaminases, which appear to be of limited clinical significance. Improvement in quality of life, weight gain and performance status was seen in both groups. Tomudex has benefits in terms of higher response rates, reduced toxicity and more frequent palliative benefits when compared with 5-FU plus LV in the management of advanced colorectal cancer, and has a more convenient administration schedule.

Key words: colorectal cancer, advanced colorectal cancer, thymidylate synthase inhibitor, chemotherapy, Tomudex, Phase III study, palliation.

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INTRODUCTION

COLORECTAL CANCER (CRC) is a common disease and an important health problem worldwide. In the European Community, the annual incidence of colorectal cancer was 32.7 per 100 000 for men and 39.4 per 100 000 for women during the period 1980–1984 [1]. In the United States in 1994, CRC was estimated to be the second most common cause of cancer deaths after lung cancer [2] and responsible for one in every 10 cancer deaths [3].

Approximately 50% of patients with colorectal cancer will

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require systemic therapy to control recurrent or disseminated disease, usually combinations of 5-fluorouracil (5-FU) and leucovorin (LV). In controlled trials, the combination of 5-FU with LV produces a significantly higher tumour response rate than 5-FU alone [4, 5] and a modest increase in survival. However, this survival advantage has not been confirmed in a meta-analysis of nine trials [6].

A recently published, randomised comparative study [7] and two reviews of the treatment of advanced CRC [8, 9] suggest that the 5-FU and low dose LV regimen, originally described by investigators at the Mayo Clinic (the North Central Cancer Treatment Group (NCCTG)), should be regarded as acceptable therapy although other 5-FU plus LV regimens appear to offer similar benefits [5, 10–14]. However, 5-FU plus LV regimens involve relatively complex scheduling of drugs, and require hospitalisation or frequent clinic visits. In addition, these regimens are associated with significant toxicity, predominantly diarrhoea, mucositis and myelosuppression. New drugs which are at least as effective as these standard regimens but which have less toxicity, greater benefits in terms of palliation, and involve a simple and more convenient dosing schedule, are clearly needed.

'Tomudex' (ZD1694) is a direct and specific thymidylate synthase (TS) inhibitor [15]. TS is a key enzyme in the *de novo* synthesis of thymidine triphosphate, a nucleotide required exclusively for DNA synthesis. Colorectal tumours are known to express TS; TS represents one of the sites of action of other antimetabolites known to have activity in CRC and other epithelial malignancies. Tomudex is a quinazoline folate analogue and enters cells rapidly by utilising the reduced folate carrier, and is then polyglutamated by folylpolyglutamate synthetase to more potent forms leading to prolonged TS inhibition, DNA fragmentation and cell death.

Phase I studies defined a recommended dose of 3.0 mg/m^2 given as a short 15 min infusion every 3 weeks [16]. Dose-limiting toxicity included diarrhoea, leucopenia, tiredness and reversible asymptomatic rises in liver transaminases. Although antitumour activity has been seen in a range of malignancies including breast, pancreatic and refractory ovarian cancer in phase II studies [17], the most striking activity was seen in advanced CRC; a phase II study involving 177 patients confirmed an objective response rate of 26% [18].

We present here the results of a randomised, open, parallel-group, phase III study comparing Tomudex intravenously (i.v.) [as a single bolus every 3 weeks] to an accepted regimen of 5-FU and low dose LV (given over 5 consecutive days every 4–5 weeks).

The study was designed to provide comparative efficacy, tolerability and safety data on the use of Tomudex as a first line single agent in the treatment of advanced CRC; primary objectives were survival, time to progression and quality of life.

PATIENTS AND METHODS

Patient selection

Patients were accrued to the study between November 1993 and June 1994. They had advanced recurrent or metastatic adenocarcinoma of the colon or rectum and had not received prior chemotherapy for advanced disease. Patients may have received adjuvant cytotoxic chemotherapy completed at least 1 year prior to entry.

Eligible patients were aged at least 18 years; had at least one measurable or evaluable lesion, a World Health Organisation (WHO) performance status of 2 or less, no other malignancies or serious illnesses, no evidence of significant renal or hepatic insufficiency, and were not receiving folic acid.

All patients gave informed consent to participate in the study and approval was obtained from an appropriately constituted ethics committee at each individual trial centre. The study was performed in accordance with the Declaration of Helsinki, and Good Clinical Practice Guidelines [19].

Treatment

Tomudex was supplied by Zeneca Pharmaceuticals, U.K., either as a solution or a lyophilised product. The contents of the vial of solution or the reconstituted lyophile were further diluted in 50 ml of either 5% dextrose or 0.9% saline and administered as a short infusion over approximately 15 min. Patients received Tomudex 3 mg/m^2 as a single dose every 21 days. 5-FU (Roche) and LV (Lederle) were administered by rapid i.v. injection. Patients received 20 mg/m^2 LV followed immediately by 425 mg/m^2 5-FU (Mayo regimen), both given once daily on 5 consecutive days. Patients were dosed every 4 weeks for the first 3 courses and every 5 weeks thereafter.

Dose modification was based on the worst grades of selected haematological toxicity (leucopenia, neutropenia, thrombocytopenia) and non-haematological toxicity (diarrhoea, mucositis, rash) seen in the previous cycle. If grade 3 or 4 toxicity occurred in patients receiving Tomudex, especially combinations of myelosuppression and diarrhoea, significant (50%) dose reductions or withdrawal from trial therapy was required. For patients receiving 5-FU plus LV, dose modifications or withdrawal followed Mayo Clinic recommendations. Treatment in both groups could be delayed by up to 21 days until all toxicity had resolved. The dose of 5-FU could be increased in the absence of toxicity. Patients with grade 3 or 4 toxicity for any of the selected effects after receiving a reduced dose were withdrawn from therapy.

Patients in either group continued therapy until disease progression or unacceptable toxicity occurred. Trial therapy could also be discontinued at the investigators' discretion.

Patient assessment

Response, time to progression, survival. In accordance with clinical practice of the majority of participating countries, patients were evaluated every 12 weeks for objective tumour response until disease progression was documented. Thereafter, all patients were followed for survival.

Objective tumour response was based on the assessment of measurable marker lesions and evaluation of non-measurable but evaluable lesions. The definitions of measurable and evaluable disease were based on recommendations by the World Health Organisation [20]. Measurements were source data validated, and response was assigned by a computer programme designed by Zeneca Biometrics Group. Complete response, partial response, stable disease or disease progression were assigned according to modified International Union Against Cancer (UICC) criteria [21]. The objective response criteria used were those recommended by the U.S. National Cancer Institute and are commonly used in large co-operative trials of colorectal cancer treatment [7, 22]. All patients who had disease progression or who died in the absence of documented disease progression were considered to have had progression events.

Patients were considered partial or complete responders if they met the above criteria and had no evidence of progression and had not died within 4 weeks of the response. All other patients were considered non-responders. All data were source data audited by study monitors.

Quality of life. Patients completed the standard 'quality of life' (QOL) questionnaire developed by the European Organisation for Research and Treatment of Cancer (EORTC) [23]. This questionnaire incorporates nine multi-item scales, comprising five functional scales (physical, role, cognitive, emotional and social), three symptom scales (fatigue, pain, nausea and vomiting) and a global health and QOL scale. It also incorporates six single questions which assessed the financial impact to the patient of the disease and a variety of physical symptoms common amongst patients with cancer (dyspnoea, sleep disturbance, appetite loss, constipation and diarrhoea). This was completed at entry and every 12 weeks until disease progression was documented.

Safety considerations. Patients were evaluated weekly for toxicity. Any detrimental change in the patient's condition, excluding progression of disease, was considered an adverse event. For all adverse events, a description of the event, its severity and duration, any treatment required, the outcome and the investigator's assessment of causality were recorded. Where applicable, adverse events were described and graded according to criteria based on WHO recommendations for the grading of acute and subacute toxic effects.

Hospital stay for treatment administration. Additional information was collected from all patients on the amount of time (recorded to nearest half day) spent by patients in hospital, as in- or outpatients, for dosing for each cycle of treatment.

Statistical methods

All analyses were performed using SAS statistical software. The study was an open, randomised, parallel-group study designed to detect a treatment difference in time to progression with at least 80% power at the two-sided alpha (5%) significance level as follows:

(a) 4 months in median time to progression if Tomudex extends time to progression relative to 5-FU plus LV.
(b) 2 months in median time to progression if Tomudex reduces time to progression relative to 5-FU plus LV.

The data cut-off for this analysis was 2 September 1994.

Randomisation was computer-generated and patients were randomised in the ratio 1:1. All efficacy analyses were performed on an intention to treat basis; the objective response analysis was also performed by treatment received. All patients were included in the analyses, irrespective of whether they were eligible or evaluable or had measurable disease. Objective responses were generated programmatically as defined above. Kaplan–Meier curves were plotted for time to progression and survival.

Time to death (survival) and time to progression were analysed using Cox's proportional hazards models. The results of the analyses were expressed as hazard ratios (Tomudex to 5-FU plus LV), 95% confidence intervals (CIs) and associated P values. The proportion of responders (i.e. patients with complete or partial best overall objective response) in the two groups were compared using a logistic regression model. The results of the analysis were expressed as an odds ratio (Tomudex to 5-FU plus LV), 95% CI and associated P value. Quality of life was analysed for each dimension separately. The changes from baseline to weeks 12 and 24 were compared between treatments using either an analysis of variance or the proportional odds model (in the case of data which were not normally distributed). The reported treatment effects were adjusted for the following covariates: prior adjuvant chemotherapy, performance status, measurable disease, gender, age and race. No treatment by covariate interaction and no departure from the assumption of proportional hazards were detected.

RESULTS

A total of 439 patients were recruited to the trial, 223 were randomised to Tomudex and 216 to 5-FU plus LV. 222 patients received Tomudex and 212 patients received 5-FU plus LV. 6 patients did not receive therapy as randomised: 1 patient was randomised to 5-FU plus LV but received Tomudex in error; 1 patient was randomised to 5-FU plus LV but received only 5-FU; a further 4 patients, 2 randomised to each treatment group, did not recieve therapy due to violation of the entry criteria, withdrawal of consent or deterioration or death prior to treatment.

Patients' characteristics are presented in Table 1. Thirty five per cent of patients receiving Tomudex and 37% of patients receiving 5-FU plus LV had one or more of the following poor prognostic factors: liver metastases ≥ 50 cm^2 in total area, liver lesion $\geq 5 \times 5$ cm^2 or performance status ≥ 2. Such prognostic factors are known to have a negative impact on prognosis [24, 25]. The two groups were well matched in terms of their demographics, previous cancer therapy, performance status and sites of disease at entry and there was no evidence of any allocation bias.

Efficacy

At the time of this analysis, the mean duration of follow-up was 5.3 months. Over 50% of patients had either progressed

Table 1. Patients' characteristics (by randomised therapy)

		Tomudex (n = 223) n (%)		5-FU plus LV (n = 216) n (%)	
Age (years)	Mean	61		61	
	Range	27 to 82		27 to 80	
Gender	Male	133	(60)	127	(59)
	Female	90	(40)	89	(41)
Race	Caucasian	214	(96)	210	(97)
	Other	9	(4)	6	(3)
WHO PS	0	101	(45)	84	(39)
	1	99	(44)	106	(49)
	2	23	(10)	26	(12)
Disease site	Liver	173	(78)	168	(78)
	Lung	56	(25)	62	(29)
	Lymph nodes	46	(21)	43	(20)
	Colon/rectum	31	(14)	29	(13)
	Local recurrence	30	(14)	33	(15)
	Skin/soft tissue	9	(4)	9	(4)
	Bone	5	(2)	11	(5)
	Other	32	(14)	35	(16)
Patients with at least one measurable lesion		216	(97)	204	(94)
Previous cancer therapy					
Surgery only		156	(70)	156	(72)
Adjuvant chemotherapy		12*	(5)	10†	(5)
Radiotherapy		33*	(15)	25†	(12)

* 6 patients received adjuvant chemotherapy and radiotherapy. † 4 patients received adjuvant chemotherapy and radiotherapy.

(55–59%) or died (23–25%) and the data are considered to be sufficiently mature to allow conclusions to be drawn from safety, objective response and time to progression data.

Objective tumour response. Table 2 summarises the overall objective response rate. There was a higher response rate in the patients receiving Tomudex than in the patients receiving 5-FU plus LV. By analysis of the data according to treatment received, the odds ratio of Tomudex to 5-FU plus LV was 1.7 with a 95% CI of 0.98–2.81 ($P = 0.059$), implying that on average, patients receiving Tomudex are 1.7 times more likely to achieve an objective response than those receiving 5-FU plus LV. These findings were confirmed in the intention to treat analysis of response where the odds ratio of Tomudex to 5-FU plus LV was 1.6 with a 95% CI of 0.93–2.66 ($P = 0.090$).

5 patients who received Tomudex and 4 patients who received 5-FU plus LV had a complete response. All patients who had complete responses had regression of liver metastases, and one patient who received 5-FU plus LV also had regression of lung metastases. All objective responses in the group receiving Tomudex occurred in patients with measurable lesions, while one of the complete responses and two of the partial responses in the group receiving 5-FU plus LV occurred in patients who had evaluable disease only.

In addition, more Tomudex patients (9.5%) than 5-FU plus LV patients (2.8%) had reductions of between 40 and 50% in the size of their measurable lesions, suggesting some additional antitumour activity, although these patients were considered non-responders in the efficacy analyses.

10 patients in each group were known to have received 5-FU containing adjvuant therapy. 3 of these patients in the group which received Tomudex and 1 patient in the group which received 5-FU plus leucovorin achieved objective response. Although the patient numbers were small, the results suggest that prior 5-FU containing adjuvant chemotherapy does not necessarily preclude a subsequent response to Tomudex.

Time to progression. A Kaplan–Meier probability plot of time to disease progression is shown in Figure 1. The hazard ratio of Tomudex to 5-FU plus LV was 1.07 (95% CI 0.83–1.37, $P = 0.612$). There was, therefore, no evidence of a statistical difference in time to progression between the two treatment groups. The median time to disease progression for patients randomised to Tomudex was 144 days with a 95% CI of 90–165 days. In the group receiving 5-FU plus LV the median time to progression was 105 days, with a 95% CI of 91–165 days.

Table 2. Overall objective response (by treatment received)

	Number (percentage) of patients	
	Tomudex ($n = 222$) n (%)	5-FU plus LV ($n = 212$) n (%)
Responders:		
Complete response	5 (2.3)	4 (1.9)
Partial response	39 (17.6)	23 (10.8)
Overall response	44 (19.8)	27 (12.7)
Minor responders:		
40–49.9% decrease in tumour size*	21 (9.5)	6 (2.8)

* These patients were considered non-responders in analyses.

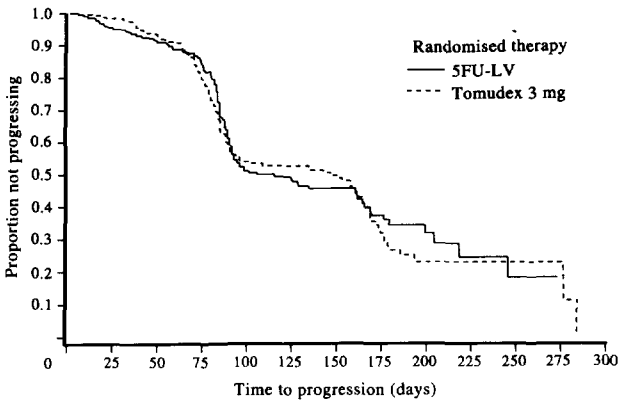

Figure 1. Kaplan–Meier probability of time to progression.

Although the median time to progression was calculated for each treatment group, the medians were not representative, as they are dependent upon the shape of the curve, which in this case reflects the timing of the objective assessments (every 12 weeks).

Survival. A Kaplan–Meier plot of time to death is shown in Figure 2. There was no evidence of a statistically significant difference between the two groups in terms of time to death; the hazard ratio of Tomudex to 5-FU plus LV was 0.84 (95% CI 0.57–1.24, $P = 0.374$). At the time of this analysis, median survival had not yet been reached.

Quality of life. Data on the rates of completion of questionnaires, and results of the statistical analysis are shown in Table 3. There was no statistically significant difference between the two groups in terms of any QOL dimension. For both groups, there was an improvement from baseline in emotional functioning, pain, sleep disturbance and global QOL.

Interestingly, baseline QOL scores impacted on later changes; patients with a good QOL score at baseline were more likely to deteriorate than patients with a poor QOL score at baseline. The latter were more likely to have an improvement in their scores. Statistical analyses were adjusted for this effect which has been described by Scheithauer and associates [26].

Other palliative effects. Although there were no statistically significant differences between Tomudex and 5-FU plus LV patients in terms of weight gain or performance status, slightly more patients receiving Tomudex showed a weight gain (15%)

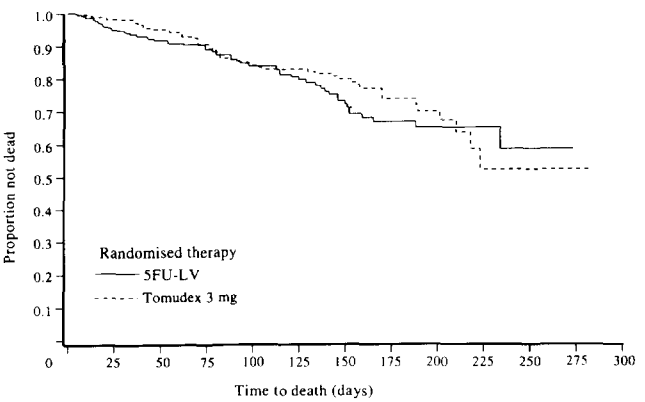

Figure 2. Kaplan–Meier probability of time to death.

Table 3. Quality of life questionnaire

Completion rate

Timepoint	Completion	Tomudex	5-FU plus LV
Baseline	Number expected	223	216
	Number completed (% of expected)	216 (97)	203 (94)
Week 12	Number expected	142	143
	Number completed (% of expected)	125 (88)	119 (83)
Week 24	Number expected	42	34
	Number completed (% of expected)	41 (98)	27 (79)

Results

Dimension	Change from baseline	Significance level (Tomudex versus 5-FU plus LV)
Physical*	—	ns
Role*	—	ns
Financial impact*	—	ns
Dyspnoea*	—	ns
Sleep disturbance*	Improved	ns
Appetite loss*		ns
Constipation*	—	ns
Diarrhoea*	—	ns
Emotional†	Improved	ns
Cognitive†		ns
Social†	—	ns
Global QOL†	Improved	ns
Fatigue†	—	ns
Nausea + Vomiting†	—	ns
Pain†	Improved	ns

* Proportional odds analysis of changes from baseline. † Analysis of variance of changes from baseline. ns, not significant.

than those receiving 5-FU plus LV (12%). Of the patients with a baseline performance status of 1 or 2, 34% of those receiving Tomudex and 25% of those receiving 5-FU plus LV had an improvement in performance status.

Hospital stay for treatment administration. The dosing frequency of Tomudex was one i.v. dose every 3 weeks. Patients receiving Tomudex spent a mean of 0.7 days per course in hospital for dosing. However, the 5-day 5-FU and LV dosage was an i.v. dose of two drugs, administered on 5 consecutive days at 4 week and after three cycles, at 5 week intervals, resulting in a mean of 3 days per course spent in hospital for dosing.

Safety

A total of 1135 cycles of Tomudex therapy were administered to 222 patients with a median of four cycles per patient (range 1–12 cycles). A total of 715 cycles of 5-FU plus LV were administered to 212 patients with a median of three cycles per patient (range 1–8 cycles). 165 (74%) patients treated with Tomudex and 111 (52%) of the patients receiving 5-FU plus LV were able to receive their treatment on time, without significant dose reduction or delay.

Adverse events and laboratory abnormalities. Severe or WHO grade 3 or 4 adverse events, irrespective of causality, occurring in at least 2% of patients are presented in Table 4. World Health Organisation (WHO) grade 3 or 4 oral effects (mucositis) were reported for 22% of patients receiving 5-FU plus LV and for 2% of patients receiving Tomudex. This difference was highly statistically significant. The incidence of grade 3 or 4 diarrhoea was similar in both groups.

Grade 3 or 4 leucopenia was statistically significantly more common in the group which received 5-FU plus LV (26%) than in the group which received Tomudex (10%). Increases in transaminases (grade 3 or 4) were reported for 10% of patients receiving Tomudex and 0% in patients receiving 5-FU plus LV. This difference in incidence was statistically significant. These transaminase elevations were more commonly seen in patients who had abnormal baseline transaminase levels or hepatic metastases but no other predictive factors were evident. However, the majority of these increases were resolving or had resolved at the end of the follow-up, and appeared to be of limited clinical significance: only 2 patients were withdrawn from trial therapy because of these increases in transaminase levels. Figure 3 shows AST and ALT levels by cycle in the patients who had WHO grade 4 increases in transaminase levels. Abnormalities of renal function were uncommon in either group.

Severe asthenia syndromes were reported for 10 (5%) patients receiving Tomudex and 4 (2%) patients receiving 5-FU plus LV; this difference was not significant. Rashes were seen with equal frequency in both groups.

Table 4. Grade 3 or 4 or severe adverse events irrespective of causality occurring in 2% or more of patients

Event	Number (percentage) of patients Tomudex (n = 222) Grades 3 and 4 n (%)	 5-FU plus LV (n = 212) Grades 3 and 4 n (%)	P value
Anaemia	11 (5)	3 (1)	0.054
Leucopenia	22 (10)	56 (26)	<0.001
Thrombocytopenia	7 (3)	1 (1)	0.068
ALT and/or AST increased	22 (10)	0 (0)	<0.001
Oral effects (mucositis)	5 (2)	46 (22)	<0.001
Diarrhoea	29 (13)	25 (12)	0.772
Nausea and vomiting	27 (12)	18 (9)	0.270
Fever	6 (3)	4 (2)	0.752
Infection	11 (5)	11 (5)	1.000
Constipation	6 (3)	6 (3)	1.000
Pain	9 (4)	14 (7)	0.286
Asthenia	10 (5)	4 (2)	0.174

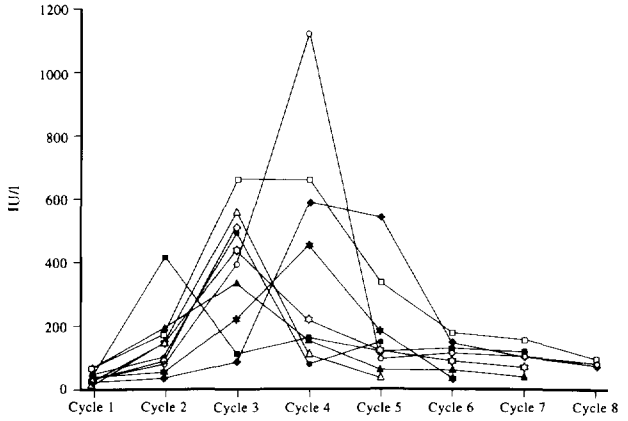

Figure 3. WHO Grade 4 increases in ALT or AST in patients receiving Tomudex. Each line represents an individual patient.

Alopecia is not listed in Table 4 as grade 3 or 4 alopecia occurred in 2% or less of patients. Overall, alopecia was reported more frequently in patients receiving 5-FU plus LV (12%) compared with those receiving Tomudex (4%).

An increase in drug-related toxicity was seen in older patients and in patients with mild to moderate renal impairment who were receiving either Tomudex or 5-FU plus LV. Increased toxicity was also seen in female patients receiving 5-FU plus LV (Table 5), confirming observations by other workers [27].

7 patients (3.2%) who received Tomudex and 5 patients (2.4%) who received 5-FU plus LV died from possible drug-related causes. In both groups, drug-related deaths appeared to be related to combinations of gastrointestinal toxicity (diarrhoea in patients who received Tomudex and mucositis in patients who received 5-FU plus LV) and myelosuppression. Of note, in the group which received Tomudex, all 7 patients who died had diarrhoea and leucopenia, with the onset of diarrhoea preceding leucopenia, although the terminal event was frequently related to leucopenia and infection. Five of the seven drug-related deaths in the group which received Tomudex occurred in patients who had experienced previous toxicity but did not receive dose reductions as specified in the protocol. This was in contrast to the deaths in 5-FU plus LV patients, all of whom were dosed in accordance with the protocol.

DISCUSSION

Current chemotherapeutic regimens using 5-FU based combination regimens have demonstrated benefits in terms of improvements in response rate, QOL and survival when compared to 5-FU alone. Two studies from the Mayo Clinic [4, 10] demonstrated that the low dose 5-FU plus LV regimen offers a survival and response advantage over 5-FU alone and it is now regarded as an acceptable combination for the treatment of advanced CRC [8]. Despite these encouraging results, the clinical benefits to patients are relatively small and the investigation of new agents with improved efficacy, better toxicity profiles or more convenient administration schedules is appropriate.

Tomudex is the result of a research programme [28] designed to develop novel drugs with direct and specific TS inhibitory effects. The non-specific effects of other commonly used antimetabolites on purine metabolism and RNA synthesis are believed to contribute significantly to toxicity; specific TS inhibition may reduce these effects. Tomudex is extensively polyglutamated, resulting in prolonged intracellular retention, which permits a convenient dosing schedule of a single, i.v. injection once every 3 weeks [29].

In this study, Tomudex showed some benefit over 5-FU plus LV in terms of objective response and its toxicity profile. The objective response rate of patients receiving Tomudex was 19.8% compared with 12.7% in patients receiving 5-FU plus LV; the odds ratio of Tomudex to 5-FU plus LV was 1.7, with 95% CI 0.98–2.8. However, there were no statistically significant differences in time to progression or survival between the two treatment groups.

Both groups experienced improvement in QOL, although the QOL analyses showed no statistically significant difference between the two groups in terms of improvement. The failure to demonstrate a significant advantage in QOL for Tomudex compared to 5-FU plus LV, despite significantly lower incidences of distressing toxicity such as mucositis, may well be real and reflect the difficulty of demonstrating differential QOL changes. However, some flaws in trial methodology may have impacted on the results: patients who received Tomudex were more likely to complete the questionnaire at the time of dosing (due to the 3-weekly cycling) and the questionnaire directly assesses toxicity symptoms seen somewhat more commonly in patients receiving Tomudex (tiredness, nausea and vomiting)

Table 5. Serious adverse events during treatment with Tomudex or 5-FU plus LV—age group, gender and serum creatinine level at entry

	Age group						Gender				Serum creatinine			
	Tomudex (n = 222)			5-FU plus LV (n = 212)			Tomudex (n = 222)		5-FU plus LV (n = 212)		Tomudex* (n = 222)		5-FU plus LV (n = 212)	
Abnormal	<60 n = 91 %	60–69 n = 82 %	≥70 n = 49 %	<60 n = 85 %	60–69 n = 80 %	≥70 n = 47 %	Female n = 90 %	Male n = 132 %	Female n = 87 %	Male n = 125 %	Normal n = 204 %	Abnormal n = 17 %	Normal n = 198 %	Abnormal n = 14 %
Fever	6.6	8.5	14.3	4.7	5.0	4.3	8.9	9.1	5.7	4.0	9.3	5.9	5.1	0.0
Asthenia	4.4	3.7	6.1	1.2	5.0	6.4	3.3	5.3	5.7	2.4	4.4	5.9	4.0	0.0
Mucous membrane disorder	0.0	1.2	4.1	2.4	5.0	12.8	2.2	0.8	9.2	3.2	1.5	0.0	6.1	0.0
Diarrhoea	8.8	14.6	22.4	10.6	8.8	2.1	13.3	14.4	10.3	6.4	12.3	35.3	8.6	0.0
Leucopenia	3.3	7.3	6.1	3.5	12.5	8.5	6.7	4.5	11.5	5.6	5.4	5.9	8.6	0.0
Nausea	7.7	7.3	14.3	7.1	5.0	6.4	8.9	9.1	5.7	6.4	8.8	11.8	6.1	7.1
Vomiting	8.8	14.6	18.4	12.9	8.8	0.0	16.7	10.6	6.9	9.6	12.7	17.6	9.1	0.0

* Data missing for 1 patient.

but does not directly assess toxicity symptoms more common in 5-FU plus LV patients such as mucositis and leucopenia.

In both groups, palliation in terms of weight gain and improvement in performance status was seen. The simple, convenient administration schedule for Tomudex reduces the associated hospital and or nursing time for reconstitution and administration, which coupled with a reduction in the number of patients visits per treatment cycle suggest that costs associated with treatment may be reduced, if compared to current 5-FU plus LV regimens.

Although the response rates seen with 5-FU plus LV were lower than some reported in the literature, they are comparable with many [10, 30–33] recently reported. In addition, the efficacy analyses in this study were performed according to the stringent criteria defined in the protocol, assessments were made every 3 months, and analyses included all patients, irrespective of evaluability or eligibility. A high proportion of patients (90%) had measurable disease and around 35–37% had poor prognostic indicators.

The tolerability profile of Tomudex compares favourably with that of 5-FU plus low dose LV. Tomudex treatment was associated with a statistically significantly lower incidence of toxicities such as grade 3 or 4 leucopenia and severe mucositis; lower incidences of any grade of alopecia were also observed, although alopecia was not common in either arm. The incidence of grade 3 or 4 increased transaminase concentrations was significantly higher in the Tomudex group, but these elevations were reversible and asymptomatic and appeared to be of limited clinical significance. In addition, Tomudex necessitated fewer dose modifications or delays than the 5-FU plus LV regimen.

Drug-related death rates were similar in the two arms of the study. However, it is likely that with increasing familiarity with Tomudex, drug-related deaths should decrease as noted with 5-FU plus LV regimens [7].

Tomudex therefore appears to offer similar advantages in terms of objective response, time to progression and survival as 5-FU and low dose LV, but in addition has benefits in terms of significantly reduced mucositis and leucopenia and good palliative effects. Tomudex has a simple and convenient dosing schedule and offers a new chemotherapeutic option for the management of advanced CRC.

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