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Klinik Çalışma / *Original Article*

Raltitrexed concomitant with radiotherapy as neoadjuvant treatment in patients with locally advanced rectal carcinoma: a phase II study

Lokal ilerlemiş rektal karsinomalı hastalarda preoperatif radyoterapi ile birlikte verilen önerilmiş dozdaki *raltitrexed*'in tedaviye cevabı

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OBJECTIVES

We aimed to evaluate the treatment response and toxic effects of the recommended dose of raltitrexed when delivered concurrently with preoperative radiotherapy in patients with locally advanced rectal carcinoma.

METHODS

This open-labeled, prospective and non-comparative study was conducted with 49 patients. Radiotherapy (50.4 Gy) was delivered in 1.8 Gy daily fractions five times per week for 5-6 weeks. Single doses of 2.6 mg/m^2 raltitrexed were infused over 15 minutes 1 hour prior to radiotherapy on days 1 and 22. Treatment response and toxicity were clinically assessed by hematological and biochemical tests and World Health Organization performance status scoring.

RESULTS

Overall treatment response was 42.9%. Post-treatment resectability opportunity was achieved in 67.3% patients. Raltitrexed was found to be related to 52.6% of the total adverse events.

CONCLUSION

The combination of raltitrexed and radiotherapy appears promising as neoadjuvant therapy in patients with inoperable rectal cancer with higher but manageable gastrointestinal toxicity.

Key words: Rectal cancer; raltitrexed; radiotherapy; survival; toxicity.

AMAÇ

Bu çalışmada, lokal ilerlemiş rektal karsinomalı hastalarda preoperatif radyoterapi ile birlikte verilen önerilmiş dozdaki *raltitrexed*'in tedaviye cevabı ve toksik etkileri değerlendirildi.

GEREÇ VE YÖNTEM

Bu açık-etiketli, prospektif ve karşılaştırmalı olmayan çalışma 49 hasta üzerinde yürütüldü. 50.4 Gy radyoterapi 5-6 hafta süreyle haftada 5 kere 1.8 Gy'lik fraksiyone dozlar şeklinde verildi. Tek doz şeklinde 2.6 mg/m^2 *raltitrexed* 1. ve 22. günlerde radyoterapiden 1 saat once 15 dakika süreyle infüze edildi. Tedaviye cevap ve toksisite klinik olarak hematolojik ve biyokimyasal testler ve Dünya Sağlık Örgütü performans skoru ile değerlendirildi.

BULGULAR

Tüm tedavi cevabı %42.9 idi. Tedavi sonrası rezektabilite oranı hastaların %67.3'ünde görüldü. Toplam *advers* olayların %52.6'sı *raltitrexed*'e bağlı bulundu.

SONUÇ

İnoperabl rektal kanserli hastalarda *raltitrexed*-radyoterapi birleşimi yüksek oranda ancak tedavi edilebilir gastrointestinal toksisite ile birlikte ümit verici bir neoadjuvan tedavi olarak gözükmektedir.

Anahtar sözcükler: Rektal kanser; raltitrexed; radyoterapi; yaşam süresi; toksisite.

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Significant advances in the treatment of colorectal cancer (CRC) have been made in recent years. Among the most striking development is the use of adjuvant chemotherapy following surgery in patients with colon cancer.[1,2] The value of chemotherapy as palliative treatment for metastatic disease has also been established.[3] Moreover, randomized trials of chemotherapy against best supportive care have provided strong justification for the use of chemotherapy in the management of advanced CRC (aCRC).[4]

In the last few years, encouraging results have been reported for preoperative chemoradiation in resectable rectal cancer.[5] Early use of chemotherapy in patients with aCRC provides effective palliation, improves quality of life and extends survival compared with symptomatic treatment or best supportive care alone.[6] 5-Fluorouracil (5-FU) has been the standard cytotoxic drug in this setting for more than 30 years. However, in the past few years, several new chemotherapeutic agents for aCRC have been introduced, including raltitrexed.[7] In several phase II trials, preoperative chemoradiation has achieved high rates of tumor down-staging with increased feasibility of surgical sphincter preservation and with a promising rate of pathological complete response (9-29%).[8-14] Preoperative acute toxicity was generally low in these studies, but the optimal combination between drugs and radiotherapy has yet to be defined.[5]

Raltitrexed (Tomudex®), a quinazoline folate analogue acting as a specific thymidylate synthase inhibitor,[15] is currently indicated for the treatment of aCRC.[16] When given as a single agent, objective response rates and survival times with raltitrexed are similar to those reported with standard 5-FU regimen and offer a more convenient dosing schedule.[17,18] However, the results of the Medical Research Council (MRC) CR06 and PETACC-1 trials have raised concerns about its toxicity.[6] Many of the deaths reported in the MRC CR06 and PETACC-1 trials occurred in patients who had been given raltitrexed following a toxic event or in the presence of renal impairment caused by dehydration or septicemia. Furthermore, as raltitrexed was, initially, preconceived as particularly non-toxic, supportive drugs were often not given.[7]

The purpose of the present study was to evaluate the treatment response and toxic effects of the recommended dose of raltitrexed when delivered concurrently with preoperative radiotherapy in patients with locally advanced rectal carcinoma.

MATERIALS AND METHODS

Subject Population

This open-labeled and non-comparative study of raltitrexed was conducted in patients suffering from locally advanced rectal carcinoma who were recruited between December 2002-December 2005 upon their admission to the Oncology Department, SB Okmeydanı Hospital, Istanbul, Turkey. The inclusion and exclusion criteria for the study are listed in Table 1. Initially, the patients with inoperable, recurrent rectal carcinoma were also included in the study; then, the study continued with only locally advanced rectal carcinoma patients due

Table 1

Inclusion and exclusion criteria of the study

Inclusion criteria

- Diagnosis of a locally advanced rectal carcinoma
- Age ≥18 years
- Presence of at least one detectable lesion
- WHO performance status score of <2
- Life expectancy of at least 12 weeks
- Suitable for systemic chemotherapy and pelvic radiotherapy

Exclusion criteria

- Previous history of systemic chemotherapy for advanced disease
- Previous history of local radiotherapy concerning the territory included in the study
- Remote metastases
- WBC counts <4.0 x 10^9/L (absolute neutrophil count 2.0 x 10^9/L), or platelet counts <100 x 10^9/L
- Serum creatinine levels above the upper limit of the normal range
- Serum bilirubin levels 1.25 times higher, AST and ALT values 2.5 times higher than upper limits of the normal range
- Severe medical illness threatening patient compliance and welfare of the study protocol
- Pregnancy, breast-feeding or use of contraceptive methods
- History of a previous malignancy, other than non-melanotic cancer of the skin or in situ carcinoma of the cervix
- Participation in another study

to an insufficient number of patients with recurrent carcinoma. Patients were diagnosed with locally advanced rectal carcinoma if they had tumor grades of T3, T4 or N+. A total of 49 patients were included initially in the study but only 28 completed the study. The most frequent reasons for study discontinuation were lost to follow-up (18.4%) and the presence of a severe illness (10.2%). Folic acid supplements and systemic anti-cancer treatment other than that applied in the study were restricted during the course of the study. A written informed consent was obtained from each subject following a detailed explanation of the objectives and protocol of the study, which was conducted in accordance with the ethical principles stated in the Declaration of Helsinki and approved by the institutional ethics committee.

Study Design

Demographic data of the patients were obtained and a full clinical examination was performed 21 days prior to the study. Hematological evaluation, which consisted of hemoglobin, white blood cell counts, neutrophil counts, and platelet counts was performed 14 days prior to the study and on days 8, 15, 22 29, 36, and 43. The biochemical measurements including serum total protein, albumin, total bilirubin, alkaline phosphatase, aspartase aminotransferase (AST), alanine aminotransferase (ALT), sodium, potassium, and creatinine levels were carried out 14 days prior to treatment and on days 22 and 43.

According to the treatment protocol, 50.4 Gy radiotherapy was delivered in 1.8 Gy daily fractions five times per week for 5-6 weeks. A single dose of raltitrexed was infused over 15 minutes (min) 1 hour (h) prior to radiotherapy on days 1 and 22. The recommended dose of raltitrexed was 2.6 mg/m^2. The second dose of the raltitrexed was planned to be reduced in the case of toxicity.

Treatment response and toxicity were clinically assessed by hematological and biochemical tests in accordance with World Health Organization (WHO) suggestions for acute and subacute toxicity, WHO performance status scoring and adverse events (including gastrointestinal and urinary toxicity). Adverse events were recorded and assessed for their association with treatment by the investigator on days 22 and 33. New adverse events were also recorded for 28 days following the last dose of either raltitrexed or radiotherapy. CTC grade ¾ patients were also followed up for developed adverse events if the physician considered there was a chance to achieve grade ½ status. Immediate CBC analysis was also made for the patients with severe diarrhea of ≥ Grade II. Creatinine clearance was determined in patients with abnormal serum creatinine levels by Cockcroft formula. The size of the marker lesion and clinical resectability status after the chemotherapy along with post-resectomy pathological staging were used to assess the rectal carcinoma.

Radiotherapy treatment was planned to be delayed up to two weeks if the toxicity signs (mucositis and abdominal pain together with grade II diarrhea) or renal failure (<25 mL/min creatinine clearance) appeared. The dosage of the raltitrexed was planned to be reduced in case of hematological (leukocyte, neutrophil and platelet counts) and non-hematological (diarrhea and a creatinine clearance of 25-65 mL/min) toxicity signs.

Intensive supportive therapy was applied for severe toxicity. Patients with grade III and IV diarrhea were hospitalized to compensate fluid and electrolyte loss and were treated with antibiotics particularly if leukopenia was detected. Total parenteral nutrition was administered in case of accelerated decline in serum albumin levels. Granulocyte colony-stimulating factor (G-CSF) was given in case of sustained leukopenia.

Statistical Analysis

The total number of patients was calculated to be 28 in order to enable ≥50% resectability rate with 90% power when type 1 error and type II error were considered as 0.05 and 0.10, respectively. If there were eight responses, then the study was continued to accrue 11 patients to determine the response rate with a higher statistical accuracy. If no response was observed in patients, the response rate was less than 20%; thus, the study would stop.

The database was transferred to SPSS after all errors due to double entries were corrected. Statis-

tical analysis was made using SPSS (version 9.0) with paired samples t test for the mean values. Chi-square and Fisher's tests were used for the analysis of the categorical data. Kaplan-Meier analysis was used to determine time till progression and survival rates. Data were expressed as means ± standard deviation (SD) and percent (%) where appropriate. Statistical significance was set at $p<0.05$.

Table 2

Demographics and clinical features of the study population

Gender		
Male		35 (71.4%)
Female		14 (28.6%)
Age (years)		58.55 ± 12.91
Height (cm)		167.36 ± 11.14
Weight (kg)		69.03 ± 9.38
Tomudex dose (mg)		
1st cycle		4609.33 ± 381.23
2nd cycle		4582.00 ± 382.08
Previous treatment for a malignancy		
Yes		12 (24.5%)
No		37 (75.5%)
Concomitant illness		
Yes		43 (87.8%)
No		6 (12.2%)
Physical examination		
Musculoskeletal system	Normal	44 (89.8%)
Respiratory system	Normal	49 (100%)
Gastrointestinal system	Normal	12 (24.5%)
Cardiovascular system	Normal	47 (95.9%)
Nervous system	Normal	49 (100%)
Genitourinary system	Normal	42 (85.7%)
Tumor grades		
T3-4NxM0		1 (2.0%)
T3N0M		1 (2.0%)
T3N1M		1 (2.0%)
T3N1M0		3 (6.1%)
T32N1Mx		1 (2.0%)
T3NxM		9 (18.4%)
T3NxM0		18 (36.7%)
T3NxMx		4 (8.2%)
T4NxM		2 (4.1%)
T4NxM0		1 (2.0%)

Data are shown as means ± SD or n (%).

RESULTS

Considering demographic features, a total of 49 patients (mean age: 58.55 ± 12.91 years, males: 71.4%) were enrolled in the study. The population was homogeneous in terms of age and gender. The majority of the patients (57.1%) were between 50-70 years of age. 93.5% of the patients had inoperable disease. Raltitrexed was applied accordingly without any dose reductions; thus, the doses of the drug did not show a significant difference in two consecutive treatment cycles. 24.5% of the patients stated that they had been previously treated for a malignancy. In 87.8% (n=43) of the patients, there were concomitant diseases (Table 2).

Evaluation of the Tumor

As shown in Table 2, the most frequent tumor grades among the study population were T3NxM0 (n=18; 36.7%) and T3NxM (n=9; 18.4%). The ratio of patients with T3NxMx grade was 8.2% and of those with T3N1M0 was 6.1%. The tumor region in the patients were rectum (n=32; 65.3%) and pelvis (n=1; 2%). In 16 patients, the tumor region was immeasurable. Tumor size was found to be 2.38 ± 2.46 cm and 3.26 ± 3.30 cm on two subsequent measurements in 29 patients.

Performance Status of the Patients

According to the performance scores, 57.1% of the patients were completely active in both initial screening and the 1st cycle. Another 53.1% were completely active in the 2nd cycle of the treatment. There was no statistically significant difference be-

Table 3

WHO performance status scores of the study population

	Complete activity	Limited activity	Restricted to bed	Total
Baseline	28 (57.1%)	20 (40.8%)	0 (0.0%)	48 (98.0%)
Raltitrexed 1st cycle	28 (57.1%)	19 (38.8%)	0 (0.0%)	47 (95.9%)
Raltitrexed 2nd cycle	26 (53.1%)	19 (38.8%)	1 (2.2%)	47 (95.9%)

Data are shown as n (%). χ^2 test was used for the analysis.

Table 4

Hematological parameters of the study population

	Baseline	Raltitrexed 1st cycle		Raltitrexed 2nd cycle	End of treatment
		Day-8	Day-15	Day-29	Day-43
Hemoglobin (g/dL)	13.29±2.01	11.7±2.2	11.64±1.79	11.15±1.9**	12.41±1.61++
Leukocytes (x10^9/L)	8.02±1.94	4.74±1.74	4.84±1.43	4.07±1.62*	5.13±1.51+
Neutrophils (x10^9/L)	64.67±14.79	63.89±13.91	65.19±10.83	72.43±20.71*	70.87±7.79
Platelets (x10^9/L)	300.4±107.2	278.24±106.3	240.82±87.24**	228.4±105.04**	221.37±66.8++

Data are shown as means ± SD. Paired samples test was used for the analysis.
*p<0.05 and ** p<0.001 compared to corresponding values of day 8; +p<0.05 and ++ p<0.001 compared to corresponding baseline values.

tween patients of screening and treatment cycles regarding the performance status (p=1.183) (Table 3).

Hematological and Biochemical Parameters

Table 4 summarizes the hematological values in the 1st cycle (Day-8 and Day-15), 2nd cycle and at the completion of the study in comparison to baseline values. Hemoglobin, leukocyte and platelet counts were found to be significantly decreased at the end of the treatment period when compared to baseline levels.

Considering the biochemical profile, serum total protein (6.95 ± 0.72 g/L vs 6.73 ± 0.6 g/L; p<0.01), albumin (3.83 ± 0.57 g/L vs 3.60 ± 0.72 g/L; p<0.001) and alkaline phosphatase (137.45 ± 88.6 IU/L vs 106.56 ± 74.86 IU/L; p<0.05) levels were decreased while AST (19.38 ± 8.53 IU/L vs 39.18 ± 26.29 IU/L; p<0.001) and ALT (17.02 ± 10.9 IU/L vs 50.06 ± 58.8 IU/L; p<0.01) levels were found to be increased in the 2nd cycle of the treatment (Day-22) compared to baseline values (Table 5).

Response to Treatment

At the 1st follow-up visit, computerized tomography (CT) results revealed the complete and partial clinical response rates as 14.3% (n=7) and 28.6% (n=14), respectively. In 16.3% (n=8) of the patients, no clinically significant improvement was observed. Disease progression was 6.1% (n=3). At the 1st visit, it was observed that 33 patients (67.3%) had operable disease. Thus, in these patients, tumor resection was performed. In the tumor-resected patients, the most frequent tumor grades were as follows: T3N2M0 (n=8; 16.3%), T3N0M0 (n=5; 10.2%), T2N0M0 (n=3, 6.1%), T2N1M0 (n=3; 6.1%), and T2N2M0 (n=2; 4.1%).

At the 2nd follow-up visit, the complete and partial clinical response rates were 6.1% (n=3) and 2.0% (n=1), respectively. In 2.0% (n=1) of the patients, the treatment regimen did not seem to promote a clinical improvement. Disease progression was observed in 6.1% (n=3) of the patients.

At the 3rd follow-up visit, the complete response rate was 2.0% (n=1) and disease progression was 4.1% (n=2).

At the 4th follow-up visit, five patients had disease progression. The treatment regimen did not seem to alter the clinical course in one patient (2.0%). Disease progression was detected in three patients (6.1%).

Adverse Events

From the total of 49 patients, 37 experienced adverse events such as diarrhea, nausea, abdominal pain, polyuria, leukopenia, anemia, and tachycardia, which prolonged the duration of hospi-

Table 5

Serum biochemical profile of the study population

	Baseline	Day-22
Total protein (g/L)	6.95 ± 0.72	6.73 ± 0.6**
Albumin (g/L)	3.83 ± 0.57	3.60 ± 0.72***
ALP (IU/L)	137.45 ± 88.6	106.56 ± 74.86*
AST (IU/L)	19.38 ± 8.53	39.18 ± 26.29***
ALT (IU/L)	17.02 ± 10.9	50.06 ± 58.8**
Creatinine (mmol/L)	0.91 ± 0.18	0.86 ± 0.16

Data are shown as means ± SD. Paired samples test was used for the analysis.
*p<0.05, ** p<0.01, and *** p<0.001 compared to corresponding baseline values.

talization. None of these adverse effects caused permanent disability or were life-threatening. The total number of adverse events was 97. The most frequently observed event was grade III diarrhea (17.5%). Grade II nausea was reported as the second most commonly experienced adverse event (15.5%). Of the 97 events, 43 were mild (44.3%), 43 were moderate (44.3%) and the remaining 10 were severe (10.3%). Raltitrexed was found to be related with 51 (52.6%) of the total adverse events, whereas radiotherapy was associated with 67 (69.1%) of the total events.

A severe adverse event (SAE) was observed in 14.3% (n=7) of the patients, and included death in three patients (due to metastases), life-threatening event in one patient and hospitalization or prolongation of hospitalization period in three patients. In those with SAEs (n=7), the disease recovered in two patients and was sustained in one patient.

In a total of 49 patients, 57.1% (n=28) completed the study. The major reasons for the drop-outs were failure of treatment (n=1), withdrawal of the consent (n=1), not coming to visits (n=9), presence of advanced disease (n=5), and death (n=4).

Survival Rate and Time to Progression

According to Kaplan-Meier survival analysis, the median survival rate of the study population was 23.69 months. In the total of 49 patients, four of them died (survival rates: 0.98 ± 0.02; 0.95 ± 0.03; 0.92 ± 0.04; and 0.46 ± 0.33). At the end of the 10th month, the study population consisted of 10 patients and at the end of 20th month there were three patients. The last patient died in the 22nd month. Cox regression analysis demonstrated no significant relationship between tumor resectability and the mortality rate of the patients (p>0.05) (Fig. 1).

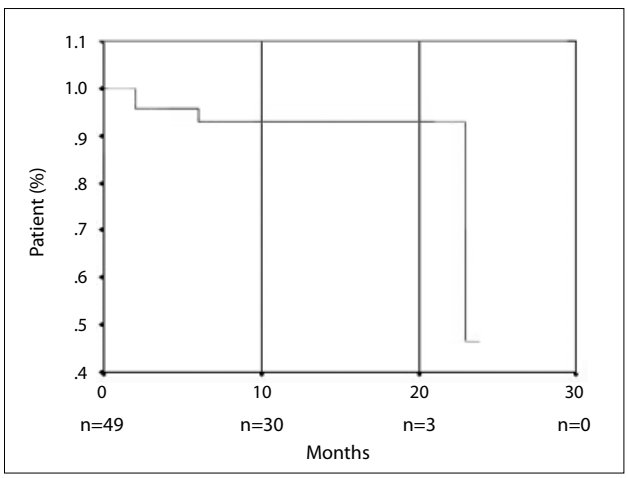

Fig. 1. Kaplan-Meier curve demonstrating the cumulative survival rate of the study population (n=49).

DISCUSSION

Raltitrexed is licensed as first-line therapy in aCRC, and has been shown to be of equivalent efficacy to the Mayo regimen of 5-FU and folinic acid.[19] As a single agent, objective response rates and survival times with raltitrexed are similar to those reported with standard 5-FU regimens but with a more reliable dosing schedule due to its administration as a single three-weekly dose by rapid intravenous infusion, thus permitting outpatient administration.[7]

Raltitrexed is generally known to be well tolerated, but potentially life-threatening side effects such as diarrhea and neutropenia should be promptly and aggressively treated and renal function should be assessed before treatment.[20]

Toxicities observed at the recommended dose of raltitrexed (2.6 mg/m^2) combined with preoperative radiotherapy were stated to be generally mild or moderate.[21] In agreement with this statement, none of the patients in this study experienced grade IV non-hematological toxicity and only one patient had a hematological toxicity of grade IV leukopenia. Transient increase in transaminases was also evident. There was no history of treatment discontinuation because of adverse events and none of our patients had impaired renal function.

Severe adverse events (SAEs) occurred in seven patients related with prolonged diarrhea and leukopenia and led to three toxic deaths. Other than toxic deaths, combination of radiotherapy with raltitrexed in our study provided the opportunity of resectability in 67.3% of the previously inoperable tumors, without need for dose reduction or cessation of treatment. The majority of the toxic effects were diarrhea (mild or moderate), nausea and leukopenia, which were managed successfully.

Our data indicate that neoadjuvant therapy

with raltitrexed plus radiotherapy resulted in preoperative clinical activity in 67% of the patients who could be evaluated in terms of new resectability opportunity. Complete treatment responses (28.6%) obtained in our study were comparable to previously stated rates of 29% and 22% with neoadjuvant therapy using the same dose of raltitrexed plus radiotherapy.[5,21]

According to local guidelines of toxicity profile, the main effects of raltitrexed concern the gastrointestinal tract, the liver and the blood. Due to its clearance via the kidneys, presence of impaired renal function or dehydration is assumed to greatly increase toxicity.[7] Based on previous studies, the expected incidences of diarrhea of grades III and IV following the first and second cycles of raltitrexed are 2.6 and 2.4%, respectively.[22]

Similar to the above statement, the most prevalent side effects of raltitrexed in the present study were grade III-IV diarrhea (15.7%) and grade II nausea (15.5%). These somewhat higher frequencies of gastrointestinal toxic effects in our study when compared to a previously stated[23] 8% incidence for diarrhea and nausea may be related to the poor gastrointestinal system status determined before the treatment protocol.

Considering raltitrexed-related gastrointestinal toxic effects in our patients, avoiding dehydration by aggressive prevention of diarrhea, nausea and vomiting seems to be crucial in prevention of the drug-related toxicity, which was stated to be increased with dehydration.[7] In accordance with this idea, all of our patients received prompt intensive supportive treatment in the event of adverse side effects.

Completion of raltitrexed treatment without a dose reduction in the present study may indicate the successful management of gastrointestinal or hematological events encountered by advanced rectal carcinoma patients, with the help of the detailed guidelines for toxicity management.

In the MRC CR06 trial comparing three different regimens in metastatic CRC, 4% of patients in the raltitrexed arm had treatment-related deaths compared to 0% in the Lokich and de Gramont arm.[24] The PETACC-1 trial[25] comparing raltitrexed with 5-FU/folinic acid in the adjuvant setting in patients with CRC was closed early because the number of drug-related deaths in the raltitrexed group was double that of the control group (1.9% vs 0.8%). In that sense, the incidence of treatment-related toxicity-related deaths (3/49) observed in our study seems to be high despite much higher rates[18] reported for combination of raltitrexed with mitomycin-C (3/22).

In the present study, the median overall survival time was 23.69 months, which was comparable to that reported for bolus 5-FU and folinic acid, and as good as that reported for the combination or 5-FU with either irinotecan or oxaliplatin.[26] Treatment response rates, number of patients achieving normal performance status and the increased resectability opportunity for the previously inoperable tumor using the combination of raltitrexed with preoperative radiotherapy in our study are comparable with those found in the phase II trials of raltitrexed.[20]

With its small sample size, our study appears to indicate that the addition of raltitrexed to radiotherapy results in increased efficacy associated with milder hematological but more frequent gastrointestinal toxicity profile, which was manageable via intensive and early supportive treatment.

In conclusion, raltitrexed and radiotherapy combination appears to be promising as neoadjuvant therapy for patients with locally advanced rectal cancer with manageable toxicity. The main drug-related toxicities were nausea, diarrhea and leukopenia, which were assumed to be preventable via strict control of fluid and electrolyte balance. Although two doses of 2.6 mg/m^2 raltitrexed was shown to be effective in increasing resectability opportunity in the present study, large-scale studies are needed to identify the optimum dose to prevent toxic [or toxicity-related] deaths in future phase II studies and to provide superior alternatives to current standard treatments.

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