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Original Article

Intensified Total Neoadjuvant Therapy in Patients With Locally Advanced Rectal Cancer: Long-term Results of a Prospective Phase II Study

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Abstract

Aims: To analyze the long-term results of a prospective phase II trial testing intensified total neoadjuvant therapy (TNT) in patients with locally advanced rectal cancer (LARC).
Materials and methods: Patients with histologically confirmed LARC adenocarcinoma were enrolled. Intensified TNT consisted of targeted agent (bevacizumab or panitumumab/cetuximab) plus FOLFOXIRI (5-fluorouracil, leucovorin, oxaliplatin and irinotecan) induction chemotherapy followed by intensified (oxaliplatin and 5-fluorouracil) chemoradiotherapy (CRT) and surgical resection. Follow-up data were collected for all patients included in the trial. Survival outcomes were calculated using the Kaplan-Meier method and curves were compared by the log-rank test.
Results: Between October 2015 and September 2019, 28 LARC patients were enrolled. Follow-up data were available for all included patients. In total, 11 (39.3%) patients had a complete response (CR). At 6.3 years (median follow-up), 5-year overall survival (OS) and DFS were 74.6% and 57.1%, respectively. Five-year OS was 80.8% for CR patients and 70.1% for no-CR patients (p-value 0.07). Those patients with CR after TNT treatment had a 5-year DFS of 81.8% versus 41.2% for those with no CR (p-value 0.015).
Conclusion: The addition of a targeted agent to induction FOLFOXIRI and oxaliplatin to 5-fluorouracil-based CRT, with the doses and intensities used in this study, resulted in high CR rates. Patients who achieve a CR demonstrate superior DFS compared to patients without CR. Intensified TNT may have the potential to increase survival outcomes. Further research on TNT strategies in LARC is encouraged.

Key words: BRAF; complete response; distant metastasis; induction chemotherapy; MSS; oxaliplatin; pCR; radiotherapy; rectal cancer; survival; total neoadjuvant therapy

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Introduction

Management of proficient mismatch repair/microsatellite stable (pMMR/MSS) locally advanced rectal cancer (LARC) (clinical stages T3, T4 or N positive) requires a multidisciplinary approach. With standard-of-care trimodality therapy, – neoadjuvant (chemo)radiotherapy followed by surgery with total mesorectal excision and adjuvant chemotherapy – local control is excellent (up to 95%), but the 5-year metastasis rate remains poor (25–35%) [1,2]. To address the distant metastasis issue, total neoadjuvant therapy (TNT) – upfront chemotherapy with six cycles of fluorouracil, leucovorin, irinotecan and oxaliplatin (FOLFIRINOX) or capecitabine and oxaliplatin (CAPOX) before (chemo)radiotherapy (induction regimen) or after radiotherapy (consolidation regimen), respectively – has been tested [3,4]. After the publication of the UNICANCER-PRODIGE 23 and RAPIDO phase III trials in 2020 [3,4], TNT became one of the new standard of care for patients with LARC, despite any improvement in overall survival (OS) [5].

Along these lines, we investigated intensified induction chemotherapy before standard of care of LARC to establish an active and feasible regimen for a phase III trial. This regimen included FOLFOXIRI (5-fluorouracil, leucovorin, oxaliplatin and irinotecan) plus bevacizumab or panitumumab/cetuximab (according to RAS-BRAF status) followed by 5-fluorouracil (5-FU) and oxaliplatin (OXP) with concomitant preoperative chemoradiotherapy (CRT) [6,7]. Here, we report the long-term outcomes of the phase II trial, which tested the use of FOLFOXIRI plus targeted agent-based induction chemotherapy and intensified CRT in LARC [7].

Methods and Materials

Study design. Full details of the design, patients' eligibility criteria and procedures have been reported previously [7,8]. In brief, this study is a prospective phase II clinical study that is registered with the Sapienza University of Rome (ethical committee number 88569-140/5638). Between October 2015 and September 2019, 28 patients were included. The primary end point was the percentage of patients achieving pathological complete response (CR). As secondary end points, 5-year overall survival (5y OS), 5-year disease-free survival (5y DFS), 5-year metastasis-free survival (5y MFS), 5-year loco-regional free survival (5y LRFS) and treatment-related toxicity were assessed.

Eligibility. Patients were eligible if they were at least 18 years of age and were diagnosed with primary LARC (cT3-4 and/or N+) within 12 cm from the anal verge, without any evidence of distant metastases. Rectal adenocarcinoma must be histologically confirmed and RAS (KRAS and NRAS) and BRAF mutational analyses performed. All patients provided written informed consent prior to participation in the study.

Treatment and study-related procedures. Treatment and procedures have been described previously [7,8]. In summary, TNT started with induction chemotherapy – four cycles of FOLFOXIRI plus bevacizumab (mutated RAS-BRAF) or panitumumab/cetuximab (wild-type RAS-BRAF). Within 6 weeks after completion of induction chemotherapy, CRT (50.4–54 Gy in 1.8 Gy/fraction) started with concomitant OXP (50 mg/m^2 on the first day of each week of radiotherapy) and 5-FU (200 mg/m^2/5 daily continuous infusions). Surgery was planned 7–9 weeks after the end of CRT and the surgical treatment approach was left to the surgeon's discretion.

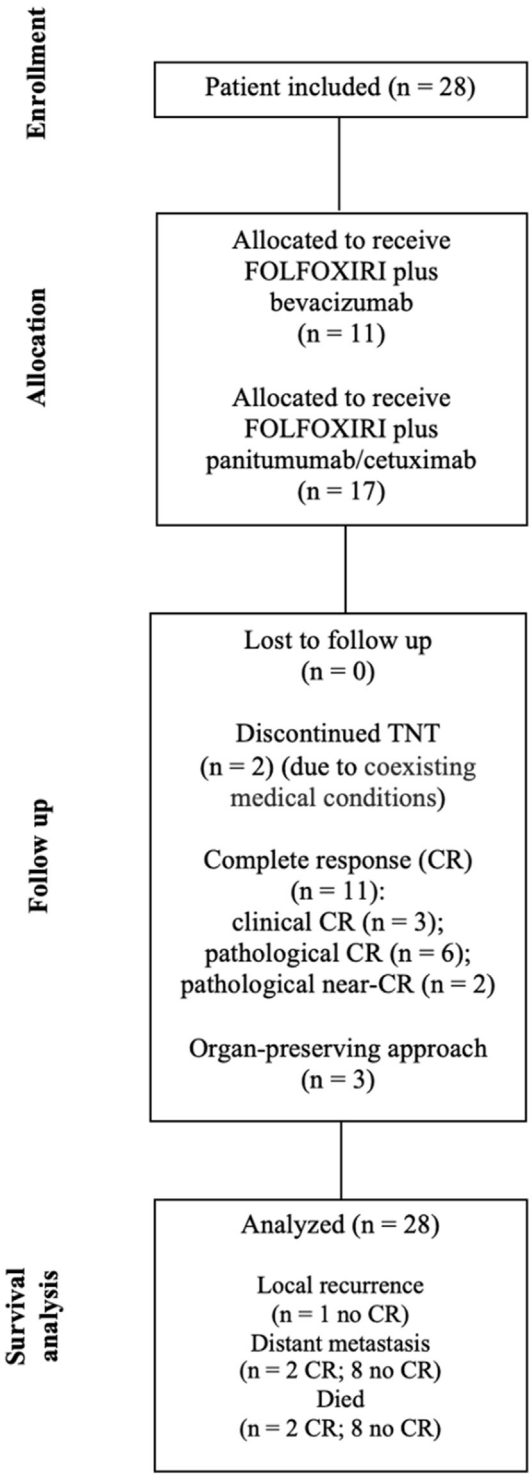
Baseline imaging of the primary tumor was performed with a pelvic diffusion-weighted magnetic resonance imaging (DW-MRI). A contrast-enhanced computed tomography (CT) scan of the chest and abdomen was used for imaging of distant metastases. Response evaluation was reassessed 2 weeks after induction chemotherapy and 5 weeks after CRT, using the same imaging procedures as were used at baseline [8].

Survival follow-up and statistics. Follow-up visits were carried out every 3 months during the first 2 years, and every 6 months thereafter, according to the policy of the institution [9,10]. Toxicity was (re)scored according to the Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0 [11]. OS, DFS, LRFS and MFS were calculated in months from the date of recruitment to the first event, including the date of the last follow-up or death (OS) and/or relapse (DFS), and/or loco-regional failure (LRFS) and/or distant metastasis (MFS). In the calculation of survival rates, patients observed to die of COVID-19 (DoC) were adjusted using CoDMI algorithm [12]. Therefore, survival rates were estimated using the Kaplan-Meier method after mean imputation (the replacement of the observed lifetime with an estimated virtual life expectancy) by CoDMI algorithm [12]. Survival curves were compared by the log-rank test. CR included patients who achieved clinical CR (on imaging re-staging after TNT) deviated from protocol and did not undergo planned surgery, patients with pathological CR defined as the absence of any residual tumor in the resected specimen and patients with pathological near-CR if small mucosal residual lesion (ypT1) occurred in the specimen. Although the preserving watch-and-wait approach was not planned in the study design, in the case of clinical CR, the decision for an organ preservation program was at the discretion of patient and, for the purpose of the study, they were considered to be included. In these cases, if patients developed recurrent disease, data would be recorded as an event in LRFS and DFS analysis.

All statistical analyses were performed using R-Studio 0.98.1091 software. A p-value of $\leq$0.05 was regarded as statistically significant. Standard descriptive statistics were used to evaluate the distribution of each variable. Continuous variables were reported as means $\pm$ 1 standard deviation (SD) and categorical variables as frequencies or percentages.

Results

Patient characteristics. Follow-up data were available for all 28 patients (Figure 1). Patient and treatment characteristics are described in Table 1.



FOLFOXIRI: 5-fluorouracil, leucovorin, oxaliplatin and irinotecan; TNT: total neoadjuvant therapy

Fig 1. Consort diagram.

Median follow-up duration was 6.3 years (range 4.4–8.2). Twenty-two patients received curative radical surgery (R0), with a conservative approach in 14 patients and Miles' excision in 4 patients. Overall, 11 patients had a CR: 3 patients showed a clinical CR, 6 patients showed a pathological CR and 2 patients achieved a pathological near-CR. Of the 6 patients who achieved a pathological CR, clinical CR on re-staging DW-MRI after finishing TNT was detected in 4 cases; of the 2 patients with pathological near-CR, both cases had a clinical near-CR on re-staging imaging.

Description of relapses. Overall, 11 patients (39%) had relapsed either loco-regionally or at the metastatic level. Seventy-three percent (n = 8) of these patients had relapsed within the first two years after the start of CRT and 91% (n = 10) within the first five years. Most relapses (n = 10; 35.7% of all patients) were distant metastasis, located in the lung (n = 2), bone (n = 3), liver (n = 2) or multiple sites (n = 3). Only one patient had experienced local failure and had undergone salvage surgery.

Disease-free survival. The overall 5-year DFS rate was 57.1% (95% CI 0.371–0.729). The CR status was strongly correlated with the risk of relapse, as depicted in Figure 2. The 5-year DFS rate was 81.8% (95% CI 0.447–0.951) and 41.2% (95% CI 0.186–0.626) for CR and no-CR patients, respectively (p-value = 0.015).

Metastasis-free survival and loco-regional-free survival. Five-year MFS for the entire population was 56.7% (95% CI 0.364–0.727). CR patients achieved better MFS rates than no-CR patients (81.8% versus 41.2%, p-value 0.018).

The overall 5-year LRFS rate was 74.1% (95% CI 0.540–0.870). Five-year LRFS among CR cases was 80.8% (95% CI 0.423–0.949) and 5-year LRFS in no-CR patients was 70.6 (95% CI 0.431–0.866) (p-value 0.065).

Overall survival and causes of death. For the OS analysis, 10 events were observed with a 5-year OS rate of 74.6% (95% CI 0.531–0.868). Most of these deaths were related to cancer, with 6 cancer-related deaths reported during the study. Two patients died due to COVID-19 infection and 2 patients due to coexisting medical conditions. Among all patients, those with CR after treatment had a 5-year OS of 80.8% (95% CI 0.423–0.949) versus 70.1% (95% CI 0.423–0.863) for those with no-CR (p-value 0.07).

Safety. The safety profile was previously described and remained unchanged [7]. There was no evidence of severe long-term toxicities. Low to moderate (grade $\leq$2) late complications had occurred in 21 patients (75 %), including gastrointestinal toxic effects (fecal incontinence = 8 cases, diarrhea = 5 cases, proctitis = 1 case) sensory neuropathy (4 cases) and genitourinary toxic effects (dysuria = 2 cases; urinary frequency = 1 case).

Discussion

In this long-term follow-up analysis of the phase II study including LARC patients, intensified TNT conferred favorable rates of survival outcomes at 5 years, without compromising local control and increasing toxicity. We demonstrated a high 5-year OS (74.6%) and relatively high 5-year DFS (57.1%), with an overall distant metastasis rate of 35.7% which is comparable to literature considering the locally advanced stages included. The addition of bevacizumab or panitumumab/cetuximab to the induction FOLFOXIRI regimen and the addition of OXP to the 5-FU regimen significantly increased both the 5-year DFS rate and the 5-

Table 1
Patient and tumor characteristics

Characteristics	No CR (n=17)	CR (n=11)	Total (n=28)	p value
Gender				0.142
male	11 (64.7%)	4 (36.4%)	15 (53.6%)	
female	6 (35.3%)	7 (63.6%)	13 (46.4%)	
Age				0.309
mean (SD)	63.59 (9.38)	58.64 (15.96)	61.64 (12.35)	
range	41.00–73.00	24.00–74.00	24.00–74.00	
Smoke				0.934
no	9 (52.9%)	6 (54.5%)	15 (53.6%)	
yes	8 (47.1%)	5 (45.5%)	13 (46.4%)	
Performance status				0.040
0	16 (94.1%)	7 (63.6%)	23 (82.1%)	
1	1 (5.9%)	4 (36.4%)	5 (17.9%)	
Comorbidity				0.264
no	3 (17.6%)	4 (36.4%)	7 (25.0%)	
yes	14 (82.4%)	7 (63.6%)	21 (75.0%)	
MMR status				/
proficient	8 (47.1%)	2 (18.2%)	10 (35.7%)	
deficient	1 (5.8%)	0	1 (3.6%)	
not available	8 (47.1%)	9 (81.8%)	17 (60.7%)	
Distance from anal verge				0.601
>8 cm	2 (11.8%)	1 (9.1%)	3 (10.7%)	
6–8 cm	9 (52.9%)	4 (36.4%)	13 (46.4%)	
<6 cm	6 (35.3%)	6 (54.5%)	12 (42.9%)	
cT				0.136
2	0 (0.0%)	1 (9.1%)	1 (3.6%)	
3	12 (70.6%)	4 (36.4%)	16 (57.1%)	
4	5 (29.4%)	6 (54.5%)	11 (39.3%)	
cN				0.636
1	2 (11.8%)	2 (18.2%)	4 (14.3%)	
2	15 (88.2%)	9 (81.8%)	24 (85.7%)	
ycT				0.018
0	0 (0.0%)	2 (18.2%)	2 (7.7%)	
2	0 (0.0%)	3 (27.3%)	3 (11.5%)	
3	10 (66.7%)	2 (18.2%)	12 (46.2%)	
4	5 (33.3%)	4 (36.4%)	9 (34.6%)	
ycN				0.492
0	3 (20.0%)	1 (9.1%)	4 (15.4%)	
1	3 (20.0%)	1 (9.1%)	4 (15.4%)	
2	9 (60.0%)	9 (81.8%)	18 (69.2%)	
yycT				0.012
0	2 (13.3%)	7 (63.6%)	9 (34.6%)	
1	1 (6.7%)	0 (0.0%)	1 (3.8%)	
2	0 (0.0%)	2 (18.2%)	2 (7.7%)	
3	9 (60.0%)	1 (9.1%)	10 (38.5%)	
4	3 (20.0%)	1 (9.1%)	4 (15.4%)	
yycN				0.677
0	6 (40.0%)	5 (45.5%)	11 (42.3%)	
1	5 (33.3%)	2 (18.2%)	7 (26.9%)	
2	4 (26.7%)	4 (36.4%)	8 (30.8%)	
Planned induction CHT				0.823
yes	15 (88.2%)	10 (90.9%)	25 (89.3%)	
no	2 (11.8%)	1 (9.1%)	3 (10.7%)	
Planned RT				0.433
yes	15 (100.0%)	11 (100.0%)	26 (100.0%)	
no	0 (0%)	0 (0%)	0 (0%)	

Table 1 (*continued*)

Characteristics	No CR (n=17)	CR (n=11)	Total (n=28)	p value
Concomitant CHT				0.781
OXP + 5FU	9 (60.0%)	6 (54.5%)	15 (57.7%)	
5FU	6 (40.0%)	5 (45.5%)	11 (42.3%)	

CR: complete response (including patological, clinical and nearly complete response); MMR: mismatch repair; c: clinical, yc: after induction chemotherapy; yyc: after neoadjuvant chemoradiotherapy; T: tumor; N: nodes; CHT: chemotherapy; RT: radiotherapy; OXP: oxaliplatin; 5FU: 5-fluoruracil.
*in ycT, ycN, yycT, yycN, planned RT and concomitant CHT rates, two cases missed due to intestinal obstruction and subsequent surgery (n = 1) and no-treatment related death (n = 1) after induction CHT.

year MFS rate in CR cases (81.8% versus 41.2% in no-CR cases), reflecting the fact that achieving a CR with intensified TNT prevent a subsequent distant relapse. However, this study was not powered to detect a statistical difference for these outcomes between CR and no-CR patients but was powered to record an improvement in CR rate (α= 0.05; β= 80%). As reported previously, the primary end point was reached with a CR rate of 39.3% (including clinical CR of 10.7%, pathological CR of 21.4% and pathological near-CR of 7.2%) [7]. To focus on the potential benefit of intensified TNT, actually, the addition of target therapy and OXP did not reduce the overall risk of systemic relapse. Indeed, the rationale to incorporate bevacizumab or panitumumab/cetuximab into induction chemotherapy and OXP into CRT treatment was mainly to improve CR rates.

Nowadays, a CR status enables an organ-preserving approach, if the CR is detected at re-staging before surgery. For sure, attention should be paid to response evaluation after TNT, and DW-MRI should be widely adopted in the re-staging assessment to offer a de-escalation treatment. In the context of expanded indications for TNT and the increased tendency of organ preservation programs in patients with CR, our scheme offers a potential opportunity for patients to refrain from surgery. The CR rate in our study (39.3%) was favorably compared to literature, irrespective of the type of TNT (induction or consolidation). In the UNICANCER-PRODIGE 23 trial, the rate of (pathological) CR was 28%, which was similar to the experimental group in the RAPIDO trial (28%) and in the STELLAR trial (21.8%) [3,4,13]. A sub-study of the RAPIDO trial compared oncological outcomes between patients with CR after TNT and CRT in the randomized setting [14]. Of the randomized patients, 137/460 (30%) patients achieved a CR in the TNT arm, whereas 66/441 (15%) achieved a CR in the CRT group (p-value <0.001). Interestingly, patient and tumor characteristics did not explain the doubled CR rate, whereas type of treatment might. For sure, it is difficult to compare these results since the TNT regimens differed between studies – differences in CHT schemes, RT dose and fractionation and use of radiosensitizer – but it is our belief that our intensified TNT strategy can be most relevant for the higher CR rate achieved. Although a better 5-year DFS rate and MFS rate were observed in the CR group, there was no significant difference in OS, but it might be revealed with a longer follow-up that will continue until 10 years.

Our study has some limitations. Firstly, the study represents the experience of a single institution. Second, this phase II study was not powered for the secondary end points reported here and the limited number of patients renders multivariate analysis irrelevant. Lastly, we did not

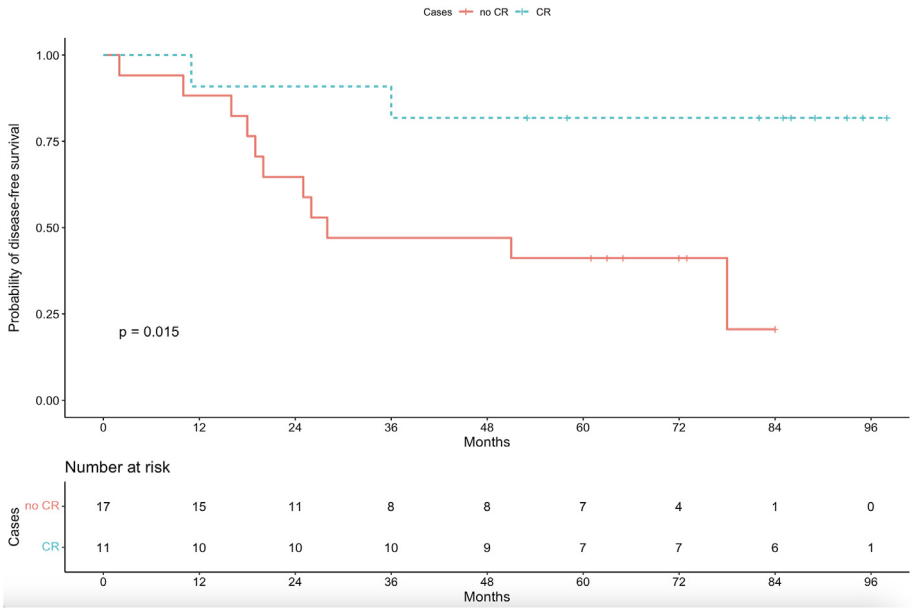


Fig 2. Disease-free survival according to complete response (CR) status.

take the potential value of the proficient or deficient mismatch repair gene expression status on inclusion criteria into account, as study design and enrollment ended before the dostarlimab as a neoadjuvant therapy benefit [15]. However, we used DWI-MRI strictly as a standard assessment tool for staging to accurately define the extent of locoregional involvement.

Overall, the results of our prospective phase II study should be interpreted with caution and do not unequivocally support the hypothesis that adding bevacizumab or panitumumab/cetuximab to the induction FOLFOXIRI and OXP to neoadjuvant 5-FU-based CRT substantially improves survival outcomes.

Conclusion

Our study confirms a high local control rate for LARC treated with the TNT approach. The adjunction of targeted agent-based induction chemotherapy and intensified CRT is warranted to increase CR rates. The use of this intensified TNT might be a way of lowering the rate of distant metastases without compromising the proper local treatment.

Author Contribution

Guarantor of integrity of the entire study: all authors
Study concepts and design: EC, FDF
Literature research: EC, FDF
Clinical studies: all authors
Data analysis/statistical analysis: LA, FDF
Manuscript preparation/editing: LA, FDF.
Final approval: all authors.

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Conflicts of Interest

The authors declare no conflict of interest.

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