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ORIGINAL RESEARCH

Safety and Efficacy of Serplulimab Combined with Neoadjuvant Chemoradiotherapy in High-Risk Locally Advanced Rectal Cancer: A Retrospective Study

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Background: Neoadjuvant chemoradiotherapy (nCRT) followed by total mesorectal excision (TME) is the standard treatment regimen for locally advanced rectal cancer (LARC). However, pathologic complete response (pCR) rates remain suboptimal, and distant metastasis remains a significant cause of treatment failure. While immune checkpoint inhibitors (ICIs) has demonstrated promising efficacy and safety in microsatellite instability-high (MSI-H) rectal cancer patients, less than 5% of rectal cancers exhibit MSI-H characteristics. The majority are microsatellite stable (MSS) types, which are generally unresponsive to immunotherapy alone. Recent studies have indicated that the addition of radiotherapy can convert immune checkpoint-insensitive "cold" tumors into more responsive "hot" tumors. Therefore, combining immunotherapy with nCRT may enhance the pCR rate and improve prognosis in LARC patients.

Objective: The study aimed to evaluate the safety and efficacy of serplulimab in combination with conventional nCRT for treating LARC, particularly in patients with high-risk factors.

Methods: A retrospective analysis was conducted using data from patients with LARC treated at the First Affiliated Hospital with Nanjing Medical University between November 2023 and July 2024. All enrolled patients received conventional radiotherapy combined with CapeOX or capecitabine monotherapy, along with serplulimab, followed by TME 8–12 weeks post-nCRT. The primary endpoint was the pCR rate, while secondary endpoints included the incidence of adverse events.

Results: A total of 29 patients were enrolled, with a median age of 60 years. About 79.3% patients had tumors located within 10 cm from the anal margin. Pre-treatment stages were uniformly categorized as IIIB or IIIC, with 51.7% classified as cT4 and 86.2% as cN2. Additionally, 65.5% exhibited tumor invasion of the mesorectal fascia. All 29 patients underwent R0 resection. Postoperative pathology revealed that 31.0% (9/29) patients achieved tumor regression grade (TRG) 0, 31.0% (9/29) patients achieved TRG 1. The most common adverse events included lymphocytopenia, fatigue, neutropenia, and anal pain. Grade 3 toxicity was observed in 48.3% of patients, with no grade 4 or 5 adverse reactions noted.

Conclusion: The combination of serplulimab with nCRT demonstrated safety and efficacy in patients with high-risk pMMR LARC. However, further verification through longer follow-up periods and large-scale prospective studies is warranted.

Keywords: locally advanced rectal cancer, neoadjuvant chemoradiotherapy, serplulimab, neoadjuvant immunotherapy, pathological complete response

Introduction

Globally, colorectal cancer (CRC) is the second most common cause of cancer-related death and the third most common cancer.[1–3] This disease burden is most noticeable in China,[4–6] where 517,000 newly diagnosed cases of CRC accounted for 26.8% of the global incidence in 2022.[7] About 83% of Chinese patients present with advanced disease at initial diagnosis, as early-stage CRC often presents with nonspecific symptoms. With only 12–22% pathological complete response (pCR) rates and 30% distant

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metastasis incidence, the standard neoadjuvant chemoradiotherapy (nCRT) followed by total mesorectal excision (TME) surgery for locally advanced rectal cancer (LARC; T3–4/N+) achieves local recurrence rates below 10% but shows limited efficacy in improving overall survival (OS).[8–10]

The treatment of metastatic colorectal cancer (mCRC) with mismatch repair deficiency (dMMR) or high microsatellite instability (MSI-H) has been transformed by immune checkpoint inhibitors (ICIs), which reverse tumor-mediated T-cell suppression to restore anti-tumor immunity.[11–13] However, dMMR/MSI-H phenotypes are present in ≤5% of rectal tumors, making ICIs ineffective for the majority of patients.[14,15] This emphasizes how urgently new treatment approaches are needed to raise pCR rates, make organ preservation easier, and increase survival.

The molecular justification for combining nCRT with ICIs comes from preclinical findings that radiotherapy causes immunogenic cell death, which promotes tumor antigen release and cytotoxic T-cell priming. Three temporal techniques have been used in recent Phase II trials investigating ICI-nCRT combinations in LARC: induction (ICIs before radiotherapy), concurrent (ICIs during radiotherapy), and sequential (ICIs after radiotherapy).[9] In microsatellite-stable (MSS) patients undergoing long-course chemoradiation (50.4 Gy + capecitabine) followed by nivolumab consolidation, the historic VOLTAGE-A study (NCT03409721) showed a 30% pCR rate (11/37), exceeding previous pCR rates of less than 20% with conventional nCRT.[16] This combinatorial paradigm is further supported by the recent multicenter NECTAR study, which used concurrent toripalimab with long-course chemoradiation and reported a 43.5% pCR rate (20/46 MSS patients).[17]

Serplulimab, a fully humanized IgG4 monoclonal antibody that specifically targets the PD-1 receptor, exhibits a distinct binding pattern to the PD-1 receptor and effectively inhibits signal transduction mediated by both PD-L1 and PD-L2.[18] In ASTRUM-015 study,[19] when serplulimab was added to the standard first-line treatment for metastatic colorectal cancer (mCRC), significant improvements in progression-free survival (PFS) and overall survival (OS) were consistently observed over a 2-year follow-up period.

Notwithstanding these developments, nothing is known about the best sequencing and safety profile of combinations based on PD-1 inhibitors. In this study, we retrospectively assess the safety and effectiveness of neoadjuvant long-course chemoradiation (capecitabine-based) in conjunction with serplulimab, in patients with LARC.

Materials and Methods

Population

From November 2023 to July 2024, we performed a retrospective cohort study of LARC patients treated at Department of Radiotherapy, the First Affiliated Hospital with Nanjing Medical University (Nanjing, China) with neoadjuvant chemoradiotherapy (CRT) + serplulimab, followed by radical resection. Pretreatment colonoscopy, contrast-enhanced chest/abdominal CT, and pelvic MRI were used to assess staging in accordance with the 8th AJCC TNM classification.

Criteria for Inclusion

(I) Rectal adenocarcinoma with histological confirmation; (II) 18–75 years old; (III) T3–4/N+ illness de novo diagnosis; (IV) tested as pMMR status by immunohistochemistry; (V) at least one of the risk factors: cT4, cN2, EMVI+,MRF+; (VI) KPS ≥70 with good hematologic, hepatic, and renal function.

Criteria for Exclusion

(I) Other malignant tumors; (II) contraindication related to radiotherapy and chemotherapy; (III) incomplete clinical and follow-up data.

This study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Jiangsu Provincial People's Hospital (No.2024-SR-732). The requirement for informed consent was waived because patient data were anonymized and retrospectively analyzed.

Protocol for Treatment

Over the course of five to six weeks, patients received intensity-modulated radiation treatment (IMRT) at 50–50.4 Gy in 25–28 daily fractions (180–200 cGy/fraction) to the primary tumor and pelvic nodal basins (mesorectum and at-risk lymph nodes).

Among the concurrent chemotherapy were as follows: A) CapeOX: Capecitabine 825 mg/m^2 BID (days 1–14) plus Oxaliplatin 130 mg/m^2 (day 1) plus serplulimab 4.5 mg/kg every three weeks OR B) Capecitabine 825 mg/m^2 BID on the day of radiotherapy plus serplulimab 4.5 mg/kg every three weeks.

Following radiation therapy, two more rounds of chemotherapy (CapeOX or capecitabine) were given. Eight to twelve weeks following the completion of CRT, surgical resection with total mesorectal excision (TME) was carried out, followed by restaging using pelvic MRI and chest/abdominal CT.

Outcomes

The study's primary objective was to determine the pCR rate, which is the percentage of surgically treated patients who achieve pCR. According to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, the secondary endpoint was the adverse events that occurred during neoadjuvant treatment. Statistical analysis was performed using the SPSS software (version 24.0, IBM).

Results

Baseline Characteristics

Fifty-two consecutive patients with LARC were admitted to the radiotherapy department between November 2023 and July 2024. After excluding 22 patients for serplulimab non-adherence (n=8), age >75 years (n=4), incomplete

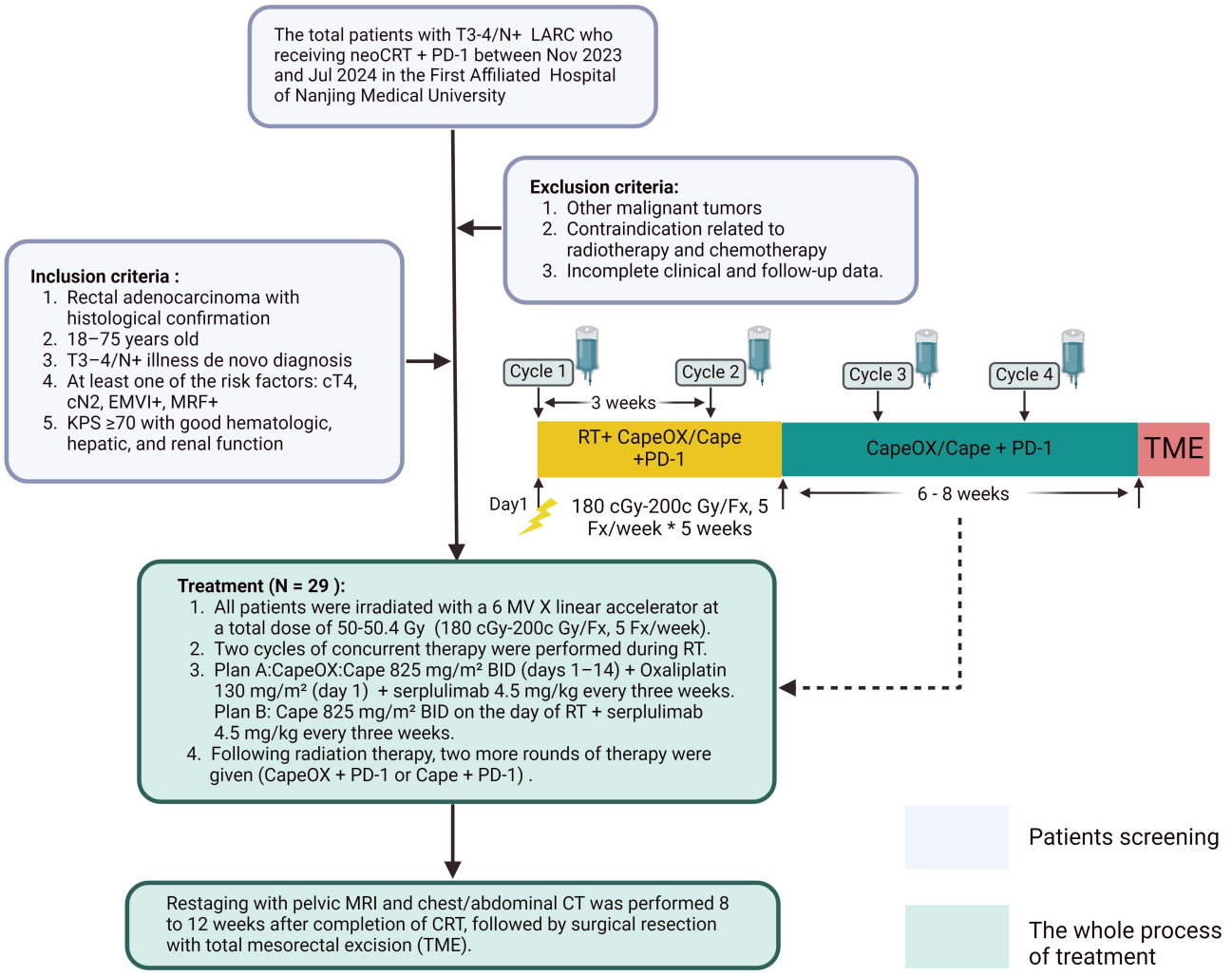

Figure 1 Study flowchart and overview of the study timeline.

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pretreatment imaging (n=4), distant metastases (n=4), or prior malignancies (n=2), 29 patients met eligibility criteria. Detailed schedules and timelines of treatments were shown in Figure 1. The characteristics of patients were shown in Table 1. Patients in the cohort had grade IIIB/IIIC (AJCC 8th edition) proficient mismatch repair (pMMR) cancers, with a median age of 60 years (range: 28–75). High-risk characteristics were common; 72.4% (21/29) had at least two risk factors, such as mesorectal fascia invasion in 65.5% (19/29), cT4 disease in 51.7% (15/29), cN2 nodal involvement in 86.2% (25/29), mid-low rectal tumors (≤10 cm from anal verge) in 79.3% (23/29), and extramural vascular invasion in 13.8% (4/29).

Evaluation of Effectiveness and Side Effects

R0 resection was achieved in every one of the 29 patients who were still having comprehensive mesorectal excision surgery. As shown in Table 2, according to pathological evaluation, 31.0% (9/29; 95% CI 27.9–34.2%) had total tumor

Table 1 Patient Characteristics

Characteristics	Patients (n = 29)
Age, years, median (range)	60 (28–75)
Sex, n (%)	
Male	21(72.4)
Female	8 (27.6)
Clinical T category, n (%)	
cT3	14 (48.3)
cT4	15 (51.7)
Clinical N category, n (%)	
cN1	4 (13.8)
cN2	25 (86.2)
Clinical disease stage, n (%)	
Stage IIIB	12 (41.4)
Stage IIIC	17(58.6)
MRF, n (%)	
Positive	19 (65.5)
Negative	10(34.5)
EMVI, n (%)	
Positive	4 (13.8)
Negative	25 (86.2)
Number of risk factors	
1	8 (27.6)
2	5 (17.2)
3	12(41.4)
4	4 (13.8)
Distance from primary tumor to anal verge, n (%)	
<5 cm	6 (20.7)
≥5, ≤10 cm	17(58.6)
≥ 10 cm	6 (20.7)
Baseline CEA level, n (%)	
Normal (≤5 ng/mL)	16 (55.2)
Abnormal (≥5 ng/mL)	12(41.4)
Unknown	1 (3.4)
Baseline CA19-9 level, n (%)	
Normal (<35 U/mL)	20(69.0)
Abnormal (≥35 U/mL)	8 (27.6)
Unknown	1 (3.4)

Table 2 Treatment Outcomes and Surgical Parameters

Description	Patients (n = 29)
Operative procedure	
Miles	4
Dixon with or without preventive colostomy	23
Hartmann	2
Pathological response	
pCR(ypT0N0), n (%)	9(31.0%)
Non-pCR, n (%)	20(69.0%)
ypT category	
ypT0	9
ypT1	1
ypT2	2
ypT3	14
ypT4	3
ypN category	
ypN0	23
ypN1	5
ypN2	1
ypStage	
yp stage 0	9
yp stage I	2
yp stage II	12
yp stage III	6
Tumor regression grade (AJCC 8th edition)	
TRG 0	9
TRG 1	9
TRG 2	10
TRG 3	1

regression (ypT0N0), 65.5% (19/29; 95% CI 62.3–68.7%) had major pathological response (TRG 1–2). The post-operative pathological remission results were shown in Figure 2.

The majority of treatment-related side events were grade 1–2 toxicities as illustrated in the Table 3, with the most common ones being fatigue (72.4%, 21/29), lymphopenia (89.7%, 26/29), and neutropenia (62.1%, 18/29). Although no

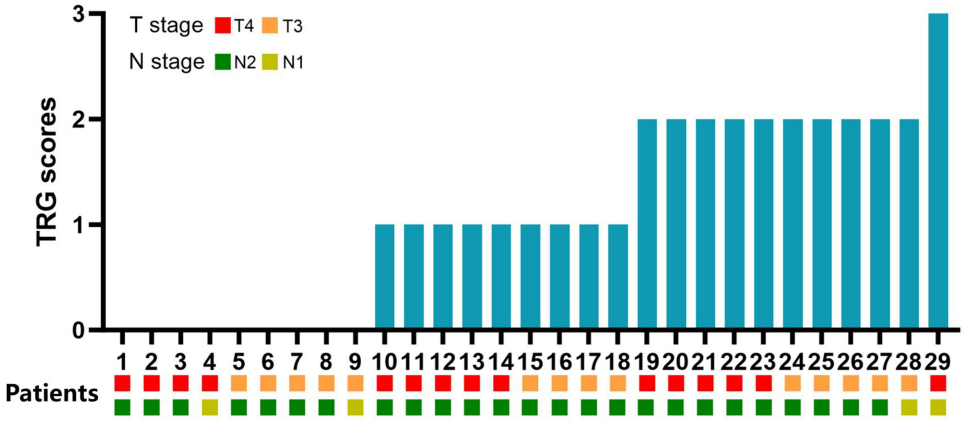

Figure 2 Histopathological tumor regression grade (TRG) per tumor in patients.

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Table 3 Acute Adverse Effects During Neoadjuvant Treatment

Adverse Event	Grades 1–2	Grade 3
Nausea	14	2
Vomiting	7	0
Fatigue	21	0
Lymphopenia	23	3
Neutropenia	16	2
Thrombocytopenia	6	5
Anemia	7	0
Increased aminotransferase level	12	0
cTnT elevation	2	0
Anal pain	14	0
Diarrhea	9	2
Tenesmus	10	0
Erythra	7	0
Increased amylase/lipase	3	0

life-threatening (grade 4/5) problems were noted, 48.3% (14/29) of patients experienced grade ≥3 events, mostly hematological toxicities (neutropenia: n=9; lymphopenia: n=5).

Discussion

Neoadjuvant CRT is still the mainstay of treatment for LARC, and survival results are greatly impacted by tumor downstaging and therapeutic efficacy.[20] ICIs have revolutionized the treatment of metastatic dMMR colorectal cancer,[14–16] but the KEYNOTE-016 (NCT01876511)[21] and KEYNOTE-028 (NCT02054806)[22] trials show little response to PD-1 monotherapy, suggesting that their usefulness in effectively treating pMMR/MSS LARC is limited. New combinatorial approaches are promising: recent phase II studies indicate that radiotherapy may enhance ICI efficacy through immunomodulation, and the NICHE trial (NCT03026140) reported 30% pathological response rates (10% pCR) in pMMR/MSS patients receiving dual nivolumab/ipilimumab neoadjuvant therapy.[23]

In pMMR/MSS LARC, this study is the first clinical assessment of serplulimab, a PD-1 inhibitor, in combination with nCRT. Three mechanisms are supported by preclinical research for the synergistic effects of radiotherapy and immunotherapy: (1) Tumor antigen presentation is improved by radiation-induced immunogenic cell death;[24] (2) The tumor microenvironment (TME) is reprogrammed to encourage CD8+ T-cell infiltration by inflammatory cytokine cascades (eg, IFN-γ, CXCL9/10);[25–27] and (3) Immunosuppressive Treg populations are selectively depleted within irradiated fields.[28,29] Our results, which show 31.0% pCR and 62.1% MPR rates, are consistent with these mechanisms and significantly higher than previous nCRT benchmarks of 12–22% pCR.[8,9] Remarkably, early clinical relief was attained by 80% of patients with obstructive symptoms, indicating quick tumor debulking.

Critical context is revealed through comparative analysis: our cohort (predominately high-risk stage IIIB/C: 51.7% cT4, 86.2% cN2) achieved comparable efficacy despite greater baseline tumor burden, whereas the Phase III UNION trial (NCT04575935)[30] reported 39.8% pCR (vs 15.3% control) using short-course radiotherapy with PD-1 inhibition. These results are supported by a 2024 meta-analysis of 533 LARC patients, which found that the pooled pCR and MPR rates for pMMR/MSS subgroups were 38% and 60%, respectively.[31] Grade ≥3 adverse events (46.7%) mirrored the TORCH study (43.8%),[32] with hematological toxicities (neutropenia: 30%; lymphopenia: 16.7%) accounting for the majority of the tolerable safety profiles.

Notably, 90% of cases of treatment-related lymphopenia need for mechanistic research. According to preclinical models, circulating lymphocytes essential for systemic antitumor immunity may be diminished by nodal irradiation.[33] In order to maintain immunological competence, future protocols might investigate reduced-field radiation that spares uninvolved lymphatics.

Our study's shortcomings include its retrospective methodology, small sample size, and lack of long-term survival data, all of which call for prospective trials to validate the findings. In conclusion, these encouraging findings demonstrate the feasibility of serplulimab-enhanced nCRT in high-risk pMMR LARC, attaining tolerable toxicity levels and pathological response rates that surpass those of traditional therapy.

Disclosure

The authors declare that they have no conflicts of interest related to this study.

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