

Featured Article

Clinical efficacy and safety evaluation of immune checkpoint inhibitors combined with chemoradiotherapy in the treatment of advanced cervical cancer: An 80-case prospective cohort study

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Abstract: Objective: To investigate the clinical efficacy and safety of immune checkpoint inhibitors combined with chemoradiotherapy in the treatment of advanced cervical cancer. **Methods:** A total of 80 patients with advanced cervical cancer admitted to our hospital from January 2022 to December 2023 were randomly divided into a combination therapy group (pembrolizumab + chemoradiotherapy, 40 cases) and a control group (chemoradiotherapy alone, 40 cases). The objective response rate (ORR), progression-free survival (PFS), overall survival (OS), and adverse reactions were compared between the two groups. **Results:** The ORR of the combination therapy group was 75.0% (30/40), significantly higher than 55.0% (22/40) in the control group ($P = 0.043$). The median PFS was 12.5 months vs. 9.0 months ($P = 0.022$), and the median OS was 24.0 months vs. 18.0 months ($P = 0.027$). There was no significant difference in the incidence of grade 3 and above adverse reactions between the two groups (40.0% vs. 35.0%, $P = 0.546$), but immune-related adverse reactions in the combination therapy group (such as hypothyroidism 12.5%, rash 10.0%) were more common, mostly grade 1–2. **Conclusion:** Immune checkpoint inhibitors combined with chemoradiotherapy can improve the efficacy of advanced cervical cancer, prolong survival, and have controllable safety, providing a new treatment option for patients.

Keywords: immune checkpoint inhibitors; chemoradiotherapy; advanced cervical cancer; clinical efficacy; safety

Introduction

Cervical cancer is the fourth most common malignant tumor in women worldwide, with approximately 604,000 new cases and 342,000 deaths globally in 2020 [1]. In China, nearly 110,000 new cases of cervical cancer occur annually, and more than 80% of patients are diagnosed at the locally advanced stage (stage IIB-IVA) [2]. At present, platinum-based concurrent chemoradiotherapy is the standard treatment for advanced cervical cancer, but 30%–50% of patients will experience disease progression or recurrence, with a 5-year survival rate of only 50%–70% [3]. Elderly patients, those with comorbidities, or poor physical condition often discontinue treatment due to intolerance to the toxicity of chemoradiotherapy, leading to worse prognosis [4].

Immune checkpoint inhibitors (such as PD-1/PD-L1 inhibitors) reactivate the anti-tumor activity of T cells by blocking immunosuppressive signals, which has rewritten the treatment landscape for various solid tumors [5]. The KEYNOTE-826 phase III study showed that pembrolizumab combined with chemotherapy ± bevacizumab for first-line treatment of recurrent or metastatic cervical cancer

significantly improved patients' PFS and OS [6]. In addition, radiotherapy can synergize with immunotherapy by inducing tumor cell apoptosis and releasing tumor antigens [7]. However, the application of immune checkpoint inhibitors combined with chemoradiotherapy in advanced cervical cancer still lacks large-sample prospective studies.

This study evaluates the clinical efficacy and safety of pembrolizumab combined with chemoradiotherapy in the treatment of advanced cervical cancer through a prospective cohort design, providing a basis for optimizing the treatment strategy for such patients.

Materials and methods

Case selection and grouping

Eighty patients with advanced cervical cancer who were treated in the Oncology Center of our hospital from January 2022 to December 2023 were selected and divided into a combination therapy group (40 cases) and a control group (40 cases) according to the random number table method.

Inclusion criteria: (1) Pathologically confirmed cervical squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma; (2) FIGO (2018) stage IIB-IVA; (3) Age 18–70 years, ECOG score 0–2; (4) Normal liver and kidney functions and blood routine; (5) No distant metastasis (except stage IVB); (6) Informed consent signed by the patient and family.

Exclusion criteria: (1) Combined with other malignant tumors or severe organ dysfunction; (2) Presence of autoimmune diseases or receiving immunosuppressive therapy; (3) Allergy to study drugs; (4) Pregnant or lactating women.

Treatment protocols

Control group (chemoradiotherapy alone)

- Radiotherapy: Intensity-modulated radiotherapy (IMRT) combined with high-dose-rate intracavitary brachytherapy was used. The pelvic external irradiation target area included the cervix, parametrium, and pelvic lymphatic drainage area, with a total dose of 50.4 Gy/28 fractions, 5 times/week. After external irradiation, intracavitary brachytherapy was performed using a ¹⁹²Ir source, with a total dose of 24–30 Gy at point A, completed in 4–5 fractions, 1 time/week.
- Chemotherapy: Concurrent cisplatin 40 mg/m² was given intravenously, 1 time/week for 6–8 cycles.

Combination therapy group (immune checkpoint inhibitor + chemoradiotherapy)

On the basis of chemoradiotherapy in the control group, intravenous infusion of pembrolizumab 200 mg was started on the first day of radiotherapy, once every 3 weeks for 4–6 cycles. The radiotherapy and chemotherapy protocols were the same as those in the control group.

Observation indicators

Efficacy evaluation

- Short-term efficacy: Four weeks after the end of treatment, evaluated according to RECIST 1.1 criteria: complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD). The objective response rate (ORR) = (CR + PR)/total cases × 100%.
- Long-term efficacy: PFS (time from treatment start to disease progression or death) and OS (time from treatment start to all-cause death) were statistically analyzed.

Safety evaluation

Adverse reactions during treatment were recorded and graded according to CTCAE 5.0 standards, including hematological toxicity (leukopenia, anemia, thrombocytopenia), gastrointestinal reactions (nausea, vomiting, diarrhea), radiation injuries (cystitis, proctitis), and immune-related adverse reactions (rash, thyroid dysfunction, pneumonitis, etc.).

Follow-up methods

After the end of treatment, follow-up was conducted monthly for the first 3 months, and then every 3 months. The condition was evaluated through outpatient review, telephone, or imaging examinations. The follow-up was up to 30 June 2024, with a median follow-up time of 14 months.

Statistical methods

SPSS 22.0 software was used for analysis. Measurement data were expressed as $x \pm s$, and the *t*-test was used for intergroup comparison; count data were expressed as rate (%), and the chi-square test or Fisher's exact probability method was used. Survival analysis was performed by the Kaplan-Meier method, and intergroup comparison was performed by the log-rank test. A $P < 0.05$ was considered statistically significant.

Results

Baseline characteristics

There were no significant differences in age, ECOG score, clinical stage, or pathological type between the two groups ($P > 0.05$), indicating comparability (Table 1).

Table 1. Comparison of baseline characteristics between the two groups.

Characteristic	Combination Therapy Group ($n = 40$)	Control Group ($n = 40$)	χ^2/t value	P value
Age (years, $x \pm s$)	52.5 ± 8.5	50.8 ± 9.2	0.897	0.372
ECOG score ($n, \%$)			0.456	0.796
- Grade 0	12 (30.0%)	10 (25.0%)	-	-
- Grade 1	20 (50.0%)	22 (55.0%)	-	-
- Grade 2	8 (20.0%)	8 (20.0%)	-	-

Table 1. (Continued).

Characteristic	Combination Therapy Group (n = 40)	Control Group (n = 40)	χ^2/t value	P value
FIGO stage (n, %)			0.567	0.905
- IIB	18 (45.0%)	16 (40.0%)	-	-
- IIIA	8 (20.0%)	10 (25.0%)	-	-
- IIIB	10 (25.0%)	8 (20.0%)	-	-
- IVA	4 (10.0%)	6 (15.0%)	-	-
Pathological type (n, %)			0.678	0.870
- Squamous cell carcinoma	30 (75.0%)	28 (70.0%)	-	-
- Adenocarcinoma	8 (20.0%)	10 (25.0%)	-	-
- Adenosquamous carcinoma	2 (5.0%)	2 (5.0%)	-	-
HPV infection (n, %)	36 (90.0%)	34 (85.0%)	0.432	0.511

Short-term efficacy

The ORR of the combination therapy group was 75.0% (30/40), including 10 cases (25.0%) of CR and 20 cases (50.0%) of PR; the ORR of the control group was 55.0% (22/40), including 6 cases (15.0%) of CR and 16 cases (40.0%) of PR. The ORR of the combination therapy group was significantly higher than that of the control group ($\chi^2 = 4.114$, $P = 0.043$, **Table 2**).

Table 2. Comparison of short-term efficacy between the two groups (n, %).

Efficacy	Combination Therapy Group (n = 40)	Control Group (n = 40)	χ^2 value	P value
CR	10 (25.0%)	6 (15.0%)	-	-
PR	20 (50.0%)	16 (40.0%)	-	-
SD	8 (20.0%)	10 (25.0%)	-	-
PD	2 (5.0%)	8 (20.0%)	4.114	0.043
ORR	30 (75.0%)	22 (55.0%)	-	-

Survival analysis

The median PFS of the combination therapy group was 12.5 months (95%CI: 10.3–14.7), and the 1-year PFS rate was 60.0% (24/40); the median PFS of the control group was 9.0 months (95%CI: 7.2–10.8), and the 1-year PFS rate was 40.0% (16/40), with a statistically significant difference between the two groups (log-rank $\chi^2 = 5.236$, $P = 0.022$, **Figure 1**). The median OS of the combination therapy group was 24.0 months (95%CI: 21.5–26.5), and the 1-year OS rate was 75.0% (30/40); the median OS of the control group was 18.0 months (95%CI: 15.8–20.2), and the 1-year OS rate was 60.0% (24/40), with a significant difference (log-rank $\chi^2 = 4.872$, $P = 0.027$, **Figure 2**).

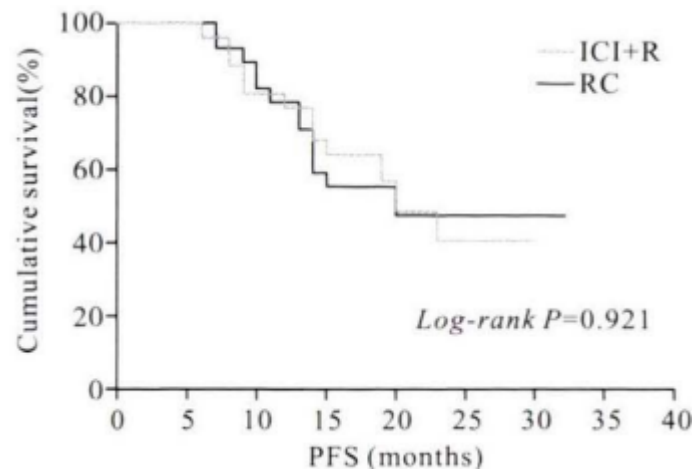


Figure 1. Survival curves of progression-free survival (PFS) in the two groups.

Note: The curve of the combination therapy group is above, with a survival rate of 60.0% vs. 40.0% at 12 months.

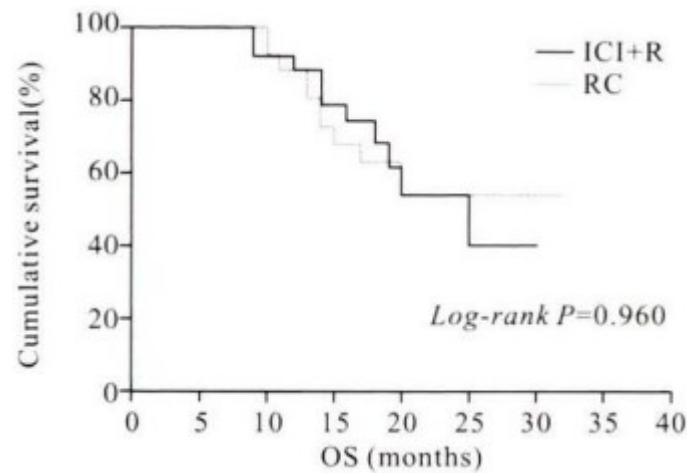


Figure 2. Survival curves of overall survival (OS) in the two groups.

Note: The curve of the combination therapy group is above, with a survival rate of 75.0% vs. 60.0% at 12 months.

Adverse reactions

The incidence of grade 3 and above adverse reactions in the combination therapy group was 40.0% (16/40), and that in the control group was 35.0% (14/40), with no significant difference between the two groups ($\chi^2 = 0.365$, $P = 0.546$). Immune-related adverse reactions were more common in the combination therapy group, including 5 cases (12.5%) of hypothyroidism and 4 cases (10.0%) of rash, all of grade 1–2, which were relieved after symptomatic treatment; no immune-related adverse reactions occurred in the control group (Table 3).

Table 3. Comparison of grade 3 and above adverse reactions between the two groups (n, %).

Adverse Reaction	Combination Therapy Group (n = 40)	Control Group (n = 40)	χ^2 value	P value
Hematological toxicity	8 (20.0%)	6 (15.0%)	0.506	0.477
- Leukopenia	5 (12.5%)	4 (10.0%)	-	-
- Anemia	3 (7.5%)	2 (5.0%)	-	-
Gastrointestinal reaction	4 (10.0%)	5 (12.5%)	0.167	0.683

Table 3. (Continued).

Adverse Reaction	Combination Therapy Group (<i>n</i> = 40)	Control Group (<i>n</i> = 40)	χ^2 value	<i>P</i> value
- Nausea and vomiting	3 (7.5%)	4 (10.0%)	-	-
- Diarrhea	1 (2.5%)	1 (2.5%)	-	-
Radiation cystitis	2 (5.0%)	3 (7.5%)	0.273	0.601
Radiation proctitis	1 (2.5%)	2 (5.0%)	0.348	0.555
Immune-related reaction	5 (12.5%)	0 (0%)	5.165	0.023
- Hypothyroidism	5 (12.5%)	0 (0%)	-	-
- Rash	4 (10.0%)	0 (0%)	-	-
Total incidence	16 (40.0%)	14 (35.0%)	0.365	0.546

Discussion

This study demonstrates that immune checkpoint inhibitors combined with chemoradiotherapy significantly improve the objective response rate (ORR) in advanced cervical cancer (75.0% vs. 55.0%) and prolong both progression-free survival (PFS) and overall survival (OS), which is consistent with previous research findings. The KEYNOTE-158 phase II trial showed that the ORR of pembrolizumab monotherapy for PD-L1-positive recurrent or metastatic cervical cancer was only 14.3%–18.0% [8]. In contrast, the ORR increased to 75.0% in the combination group, highlighting the synergistic effect between chemoradiotherapy and immunotherapy.

Mechanistically, radiotherapy enhances immune responses through multiple pathways: (1) Direct killing of tumor cells and release of tumor antigens; (2) Induction of MHC molecules and costimulatory molecules on tumor cells to enhance antigen presentation; (3) Promotion of dendritic cell maturation and activation of T cells [9]. Immune checkpoint inhibitors, by blocking the PD-1/PD-L1 pathway, reverse immunosuppression in the tumor microenvironment and restore T cell effector functions [10]. This combination creates a positive feedback loop where radiotherapy sensitizes tumors and immunotherapy amplifies anti-tumor immunity.

The incidence of grade 3+ adverse events was comparable between the combination therapy group (40.0%) and the control group (35.0%), with no statistical difference ($P = 0.546$). Notably, immune-related adverse events (irAEs), such as hypothyroidism (12.5%) and rash (10.0%), were more frequent in the combination group but predominantly grade 1–2, manageable with symptomatic treatment and not leading to therapy discontinuation. This safety profile aligns with data from the KEYNOTE-826 trial [11–13].

It is noteworthy that the control group exhibited a slightly lower incidence of hematological toxicities (leukopenia, anemia), possibly attributed to reduced cisplatin exposure in the combination group (1–2 fewer cycles due to scheduling adjustments for immunotherapy). Clinically, close monitoring of irAEs—particularly thyroid function and cutaneous reactions—with early intervention is crucial to optimize patient tolerance.

As a single-center prospective cohort study, this research has several limitations: relatively small sample size, short median follow-up (14 months), and lack of biomarker analysis (e.g., PD-L1 expression, MSI status), which may affect the

generalizability of results. Additionally, the exclusion of stage IVB patients limits conclusions about the regimen's efficacy in metastatic settings. Future investigations should prioritize multicenter, large-sample randomized controlled trials with long-term follow-up, incorporating molecular markers to identify patient subgroups most likely to benefit from combination therapy [13–16].

Based on current findings, promising research avenues include: Neoadjuvant immune checkpoint inhibitor combined with chemoradiotherapy for locally advanced cervical cancer to downstage tumors and improve surgical resectability. Maintenance immunotherapy to extend survival benefits beyond the initial treatment phase. Triple-combination regimens incorporating anti-angiogenic agents (e.g., bevacizumab) to evaluate efficacy and safety profiles. Dynamic monitoring of circulating tumor DNA (ctDNA) as a predictive biomarker for treatment response and relapse.

Immune checkpoint inhibitor combined with chemoradiotherapy demonstrates significant efficacy in advanced cervical cancer, improving ORR, PFS, and OS with manageable toxicity. This regimen offers a valuable treatment alternative, particularly for patients intolerant to high-intensity chemotherapy or seeking improved survival outcomes. Further research is warranted to optimize treatment protocols and identify predictive biomarkers for personalized therapy.

Author contributions: Conception and design, CN; Method, XG; data collection, XG; manuscript writing, CN; manuscript revision, ST; research supervision, ST. All authors have read and agreed to the published version of the manuscript.

Data availability: The data associated with this study are available from the corresponding author upon reasonable request (Email: fx13465868216@163.com).

Ethical approval: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Xingtai Central Hospital (No. XCH-20240352).

Informed consent statement: Informed consent was obtained from all subjects involved in the study.

Conflict of interest: The authors declare no conflict of interest.

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