Intensity-modulated radiation therapy (IMRT)-based concurrent chemoradiotherapy (CCRT) with Endostar in patients with pelvic locoregional recurrence of cervical cancer

Results from a hospital in the Qinghai-Tibet Plateau

Kuan Zhang, BSa, Huiping Wang, BSb, Zhengqing Wang, BSb, Fuqing Li, BSa, Ying Cui, BSa, Shengchun Ma, BSa, Rui Chen, BSa, Yuhui Wang, BSa, Shul Guo, BSa, Ying Wei, BSa

Abstract

The treatment of recurrent cervical cancer, especially pelvic locoregional recurrence, is very challenging for gynecologic oncologists. This study investigated the efficacy and safety of intensity-modulated radiation therapy (IMRT)-based concurrent chemoradiotherapy (CCRT) with Endostar, a novel modified recombinant human endostatin, in patients with pelvic locoregional recurrence of cervical cancer following surgical treatment. This phase 2 study was conducted between May 2018 and May 2019 at a single center in the Qinghai-Tibet Plateau and enrolled 31 patients with pelvic locoregional recurrence of cervical cancer following surgical treatment. All patients were treated with IMRT-based CCRT for 6 weeks and intravenous infusions of Endostar (15mg/m²), which were administered on days 1 to 7 of CCRT, followed by rest for 4 weeks. After resting, chemotherapy with cisplatin (70mg/m²) plus paclitaxel (135–175mg/m²) was given every 3 weeks for a total of 4 treatments. Thirty-one patients were evaluable for the primary endpoint. The mean age was 50.03 years (SD 7.72). The objective response rate was 67.74% and the disease control rate was 83.87% (48.39% achieved a complete response, 19.35% a partial response, 16.13% had disease stabilization, and 16.13% had progressive disease). The most common adverse events were nausea, vomiting, alopecia, neutropenia, and leukopenia; most events were grade 1 or 2 in intensity. Grade 3 toxicities included thrombocytopenia and neutropenia in 2 patients each, and leukopenia in 4 patients. No cases of grade 4 acute toxicity were observed.

IMRT-based CCRT with Endostar infusions is effective and safe. Our results support the use of this treatment for patients with pelvic locoregional recurrence of cervical cancer following surgical treatment.

Abbreviations: AEs = adverse events, CCRT = radical surgery and concurrent chemoradiotherapy, CTV = clinical target volume, GI = gastrointestinal, IMRT = intensity-modulated radiation therapy, NSCLC = non-small cell lung cancer. PTV = planned target volume, RT = radiation therapy, VEGF = vascular endothelial growth factor.

Keywords: antiangiogenesis, CCRT, cervical cancer, IMRT, pelvic locoregional recurrence

1. Introduction

Cervical cancer is the third most common cancer in women and the third most common cause of cancer-related death among women, with approximately 570,000 new cases in 2018, comprising 6.6% of all female cancers. Low- and middle-income countries reported 90% of all worldwide deaths in 2018 relating to cervical cancer. Cervical cancer is also one of the most common cancers among women in China, with around 98,900 new cases and 30,500 deaths reported there in 2015. Treatments for cervical cancer include surgery, radiation therapy (RT), and chemotherapy (CRT). Radical surgery and concurrent chemoradiotherapy (CCRT) is the standard mode of treatment worldwide and in China. However, disease recurs in approximately one-third of patients and fewer than 5% of them remain alive at 5 years after recurrence. Recurrent cervical cancer can present as a local recurrence or as metastatic disease. Local recurrence is categorized as either central recurrence (cervix or vaginal stump) or noncentral recurrence (pelvic lymph nodes or pelvic side wall). Local recurrence rates following definitive chemoradiation range between 5% and 18%. Currently, few treatment options are available for patients with noncentral recurrence, especially those with...
recurrence in the pelvic lymph nodes or pelvic side wall. Thus, the treatment of recurrent cervical cancer is very problematic.

The advent of three-dimensional radiation therapy (3D-RT) and then the more precise mode of intensity-modulated radiotherapy (IMRT) has improved the treatment of cervical cancer. Nevertheless, RT is marked by high levels of acute and chronic toxicities. The acute toxicities lower the patient’s quality of life and frequently lead to premature termination of curative chemotherapy. Novel treatment strategies are needed that have a lower burden of toxicity and are more effective.

Angiogenesis is critical in the development and metastatic spread of cancer. Targeting the angiogenic pathway helps to control disease progression in cervical cancer. Angiogenesis plays an important role in locally advanced cervical cancer, with abnormal vascular endothelial growth factor (VEGF) expression specifically associated with cervical cancer. Bevacizumab is an anti-VEGF monoclonal antibody that has proven to be an effective treatment for recurrent cervical cancer. In a case series describing the use of bevacizumab in 6 heavily pretreated patients with recurrent cervical cancer, 4 achieved a complete response, 1 had a partial response, and 2 achieved disease stabilization; treatment was reportedly well tolerated. Thus, antiangiogenic therapy shows promise in cervical cancer. Recombinant human endostatin (Endostar; YP-16) is a potent angiogenesis blocker that was granted approval in 2005 by China’s State Food and Drug Administration (SFDA) for the treatment of non-small cell lung cancer (NSCLC). Endostar improves chemotherapy efficacy in cervical cancer, but little is known about the potential advantages of combining IMRT with antiangiogenesis strategies in noncentral recurrences of this disease.

We therefore performed a single-arm phase 2 trial of IMRT-based CCRT and Endostar in a cohort of patients with pelvic locoregional recurrence of cervical cancer following surgical treatment. We evaluated the safety and efficacy of this management strategy for pelvic side wall recurrences of cervical cancer.

2. Materials and methods

2.1. Subjects

A total of 31 patients with pelvic side wall recurrences of cervical cancer following surgery were admitted by the Qinghai Red Cross Hospital between May 2018 and May 2019 and were enrolled into this study. The inclusion criteria were: age between 20 and 70 years; a Karnofsky Performance Status score of ≥70 points; a diagnosis of noncentral recurrence cervical cancer confirmed by 2 or more methods; no history of RT; no history of platinum drug allergies; laboratory findings within the following ranges (at ≤14 days prior to enrolment): hemoglobin ≥100g/L, neutrophil count ≥1.5 × 10⁹/L, white blood cell count ≥3.5 × 10⁹/L, platelet count ≥100 × 10⁹/L; creatinine ≤1.0 × upper limit of normal; alanine aminotransferase/aspartate aminotransferase ≤1.5, alkaline phosphatase ≤1.5 × UNL, total bilirubin ≤1.5 × UNL; and agreement to participate in follow-up visits. Exclusion criteria included: pregnancy or lactation, previous (<5 years) malignancy, any serious complication that would affect full compliance with treatment, mental illness, and age under 20 years. The study was approved by the Qinghai Red Cross Hospital Institutional Review Board and it was conducted in compliance with national legislation and the Declaration of Helsinki guidelines. Neither the patients nor general public were involved in the design and conduct of the study. All study participants gave written informed consent before enrollment.

2.2. Study design

This study was a nonrandomized, single-arm, single-institution, phase 2 trial for the treatment of pelvic locoregional recurrence of cervical cancer. The flow diagram of the trial is depicted in Figure 1.

2.3. IMRT details

IMRT planning incorporated computer tomography (CT)-based simulation in the supine position with knee rest. Magnetic resonance imaging (MRI) scans were obtained with an interslice distance of 5 mm, after intravenous contrast taken from the upper edge of the lumbar vertebra to a position situated at 2 cm below...
of treatment. Fifteen patients achieved a complete response (48.39%), 6 a partial response (19.35%), and 5 each had stable disease or progressive disease (16.13%). The objective response rate was 67.74% and the disease control rate was 83.87% (Table 2).

3.3. Treatment toxicities

At 1 month, no patients had died. Safety is analyzed in Table 3. The most common adverse events (AEs) (affecting ≥20 patients in either treatment group) were GI disorders (nausea, vomiting), alopecia, neutropenia, and decreases in white blood cell count. Most AEs were grade 1 or 2 in intensity; grade 3 AEs included thrombocytopenia and neutropenia in 2 patients each, and leukopenia in 4 patients. There were no cases of grade 4 acute toxicity (Table 3).

4. Discussion

Approximately 98,900 new cases and 30,500 deaths from cervical cancer were reported in China during 2015.\textsuperscript{[23]} Radical hysterectomy and pelvic lymphadenectomy has been considered to be an effective treatment program for early-stage cervical cancer.\textsuperscript{[24]} However, approximately 14% to 57% of patients experience a central recurrence after radical surgery and, depending on different risk factors, rates of pelvic recurrences fluctuate from between 10% and 74%.\textsuperscript{[26,27]} Recurrent and metastatic cervical cancer are incurable, with 1-year survival rates of between 15% and 20%.\textsuperscript{[27]} Cisplatin-based chemotherapy...
apy ameliorates symptoms and prolongs progression-free survival in cervical cancer patients. Improvements in single and combined modality treatment have increased the rates of local tumor control for cervical cancer, but locoregional recurrences after initial (surgical or radiation) treatment still occur. Our study was performed in a single center in the Qinghai-Tibet Plateau. The aim of this study was to evaluate the efficacy and safety of IMRT-based CCRT combined with Endostar in patients with pelvic locoregional recurrence of cervical cancer. Thirty-one of our patients obtained a clinical benefit after treatment, and there were no cases of grade 4 acute toxicity. This treatment schedule therefore appears to be effective and safe for patients.

Pelvic RT plays an important role in the treatment of cervical cancer. IMRT delivers a high dose of radiation to tumor tissue and restricts dose exposure to adjacent noncancerous tissue. However, the side effects of RT greatly compromise quality of life. The most common acute adverse reactions following RT are abdominal pain, diarrhea, hemorrhage, intestinal obstruction, and granulocytopenia. Many patients refuse to undergo RT because of these potential side effects. In our study, the most common AEs were nausea, vomiting, alopecia, neutropenia, and leukopenia, which were grade 1 or 2 in intensity. Thus, IMRT combined with Endostar offers meaningful protection of organs (such as the pelvis) and improves quality of life.

VEGF is critical to the growth of tumor blood vessels and is considered to be an appropriate therapeutic target in cervical cancer. In a phase 2 trial of bevacizumab in recurrent cervical cancer, 11 (23.9%) of the 46 evaluable patients achieved progression-free survival for at least 6 months with a median value of 3.40 months (2.5–4.3 months), and 5 (10.9%) attained a partial response, with a median response duration of 6.2 months (2.8–8.3 months). Median overall survival was 7.29 months (6.1–10.4 months). The use of bevacizumab in cervical cancer has proven to be effective and safe, but is very expensive to administer. Endostar exhibits significant synergistic effects with standard chemotherapy and is very cheap. The efficacy of Endostar has been proven in clinical trials of stage III NSCLC, and has been approved by China’s SFDA for use in advanced NSCLC. Hypertension, proteinuria, and hand-foot syndrome are the most common AEs associated with antiangiogenic agents. Not only is Endostar associated with a low rate of AEs but when combined with chemoradiotherapy, Endostar appears to improve early outcomes in patients with advanced cervical cancer, without AEs. Our study, although small, demonstrates good efficacy and safety of Endostar combined with CRT in the treatment of pelvic locoregional recurrence of cervical cancer. Further larger-scale clinical investigations are warranted.

As well as antiangiogenic therapy, agents targeting various biological mechanisms such as epigenetics, the epidermal growth factor receptor, poly(ADP-ribose) polymerase activity, and the mammalian target of rapamycin, represent exciting investigational opportunities. Moreover, explorations of immunotherapy approaches are indicating potential for the development of therapeutic vaccines and immune checkpoint inhibitors. All of these investigations offer new directions for patients such as those who participated in this study.

5. Conclusion
Our results appear to support the use of IMRT-based CCRT with Endostar for patients with pelvic locoregional recurrence of cervical cancer following surgery. Long-term follow-up of our study participants and further studies are needed to confirm the role of Endostar in the management of this disease.

| Table 2 | Response rates for patients with pelvic locoregional recurrence of cervical cancer following surgical treatment. |
|---------|---------------------------------------------------------------------------------------------------------|
| Evaluable patients after 1 month of follow-up | n | % |
| CR | 15 | 48.39 |
| PR | 6 | 19.35 |
| SD | 5 | 16.13 |
| PD | 5 | 16.13 |
| ORR | 21 | 67.74 | 1 |
| DCR | 26 | 83.87 | 1 |
| ORR = complete response, DCR = disease control rate, ORR = objective response rate, PD = progressive disease, PR = partial response, SD = stable disease. |
| *ORR = CR + PR. |
| †DCR = CR + PR + SD. |

| Table 3 | Most common treatment-emergent acute adverse events possibly related to study treatment in the 31 evaluable patients. |
|---------|-------------------------------------------------------------------------------------------------------|
| Adverse events | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Total |
| Gastrointestinal disorders | | | | | |
| Constipation | 17 | | | | 17 |
| Nausea | 21 | 10 | | 31 |
| Vomiting | 19 | 10 | | 29 |
| General disorders | | | | | |
| Pain | 6 | | | 6 |
| Fatigue | 16 | 3 | | 19 |
| Skin and subcutaneous tissue disorders | | | | | |
| Alopecia | 13 | 13 | | 26 |
| Pruritus | 3 | | | 3 |
| Investigations | | | | | |
| Hemoglobin increased | 8 | 2 | | 10 |
| Thrombocytopenia | 13 | 3 | 2 | 18 |
| Neutropenia | 9 | 17 | 2 | 28 |
| Leukopenia | 3 | 21 | 4 | 28 |
| Adverse events were coded using The Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. |
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Author contributions
Conceptualization: Kuan Zhang.
Data curation: Kuan Zhang, Huiping Wang.
Formal analysis: Kuan Zhang.
Funding acquisition: Kuan Zhang.
Investigation: Kuan Zhang, Huiping Wang, Zhenqing Wang, Fuqing Li, Ying Cui, Shengchun Ma, Rui Chen, Yuhui Wang, Shul Guo, and Ying Wei.
Writing: Kuan Zhang.

References
[1] Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424.
[2] Lin Y, Chen K, Lu Z, et al. Intensity-modulated radiation therapy for definitive treatment of cervical cancer: a meta-analysis. Radiat Oncol 2018;13:177.
[3] Liu X, Meng Q, Wang W, et al. Predictors of distant metastasis in patients with cervical cancer treated with definitive radiotherapy. J Cancer 2019;10:3967–74.
[4] Li H, Wu X, Cheng X. Advances in diagnosis and treatment of metastatic cervical cancer. J Gynecol Oncol 2016;27:e43.
[5] Todo Y, Watari H. Concurrent chemoradiotherapy for cervical cancer: background including evidence-based data, pitfalls of the data, limitation of treatment in certain groups. Chin J Cancer Res 2016;28:221–7.
[6] Kubota H, Tsuchino K, Sulaizam NS, et al. Comparison of salvage therapies for isolated para-aortic lymph node recurrence in patients with uterine cervical cancer after definitive radiotherapy. Int J Radiat Oncol Biol Phys 2019;101:236.
[7] Yoshida K, Kajiyama H, Usumi F, et al. A post-recurrence survival-predicting indicator for cervical cancer from the analysis of 165 patients who developed recurrence. Mol Clin Oncol 2018;8:281–5.
[8] Amin A, Sumner W, Fisher CM. Durable control and overall survival benefit with focal reirradiation in cervical cancer. Cureus 2015;7:e399.
[9] Kim TH, Kim MH, Kim BJ, et al. Prognostic importance of the site of recurrence in patients with metastatic recurrent cervical cancer. Int J Radiat Oncol Biol Phys 2017;98:i1124–31.
[10] Bryant AK, Huyhn-Le MP, Simpson DR, et al. Intensity modulated radiation therapy versus conventional radiation for anal cancer in the veterans affairs system. Int J Radiat Oncol Biol Phys 2018;102:109–15.
[11] Liaw SL, Connell PP, Weichselbaum RR. New paradigms and future challenges in radiation oncology: an update of biological targets and technology. Sci Transl Med 2013;5:173sr2.
[12] Liu Y, Yu J, Qian L, et al. Extended field intensity-modulated radiotherapy plus concurrent nedaplatin treatment in cervical cancer. Oncol Lett 2016;11:3421–7.
[13] Zuazo-Gaztelu I, Casanovas O. Unraveling the role of angiogenesis in cancer ecosystems. Front Radiat Oncol 2019;5.
[14] Lugano R, Ramachandran M, Dunberg A. Tumor angiogenesis: causes, consequences, challenges and opportunities. Cell Mol Life Sci 2019;77:1745–70.
[15] Esfahani RN, Tewari KS. Targeting angiogenesis in advanced cervical cancer. Ther Adv Med Oncol 2014;6:200–92.
[16] Tewari KS, Sill MW, Long HJ, 3rd, et al. Improved survival with bevacizumab in advanced cervical cancer. N Engl J Med 2014;370:734–43.
[17] Wright JD, Viviano D, Powell MA, et al. Bevacizumab combination therapy in heavily pretreated, recurrent cervical cancer. Gynecol Oncol 2006;103:489–93.
[18] Zhang K, Wang Y, Xu X, et al. Recombinant human endostatin combined with radiotherapy inhibits colorectal cancer growth. BMC Cancer 2017;17:899.
[19] Ke QH, Zhou SQ, Huang M, et al. Early efficacy of Endostar combined with chemoradiotherapy for advanced cervical cancers. Asian Pac J Cancer Prev 2012;13:923–6.
[20] Jia Y, Liu M, Cao L, et al. Recombinant human endostatin, Endostar, enhances the effects of chemo-radiotherapy in a mouse cervical cancer xenograft model. Eur J Gynaecol Oncol 2011;32:316–24.
[21] Dang YZ, Li P, Li JP, et al. Efficacy and toxicity of IMRT-based simultaneous integrated boost for the definitive management of positive lymph nodes in patients with cervical cancer. J Cancer 2019;10:1103–9.
[22] Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys 1995;31:1341–6.
[23] Hay JL, Atkinson TM, Reeve BB, et al. Cognitive interviewing of the US National Cancer Institute’s patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE). Qual Life Res 2014;23:237–69.
[24] Schwartz LH, Litiere S, de Vries E, et al. RECIST 1.1-Update and clarification: from the RECIST committee. Eur J Cancer 2016;62:132–7.
[25] Chen C. Cervical Cancer in China. 2020. Available at: https://www.fgco.org/news/cervical-cancer-china. Accessed February 3, 2020.
[26] Liu SP, Huang X, Ke GH, et al. 3D radiation therapy or intensity-modulated radiotherapy for recurrent and metastatic cervical cancer: the Shanghai Cancer Hospital experience. PLoS One 2012;7:e40299.
[27] Peretti M, Zaprunti I, Zanagnolo V, et al. Management of recurrent cervical cancer: a review of the literature. Surg Oncol 2012;21:e59–66.
[28] Yin YJ, Li HQ, Sheng XQ, et al. The treatment of pelvic locoregional recurrence of cervical cancer after radical surgery with intensity-modulated radiotherapy: a retrospective study. Int J Gynecol Cancer 2015;25:1038–65.
[29] Yu J, Xu Z, Li A, et al. The efficacy and safety of apatinib treatment for patients with metastatic or recurrent cervical cancer: a retrospective study. Drug Des Devel Ther 2019;13:3419–24.
[30] Zukauskaitè R, Hansen CR, Grau C, et al. Local recurrences after curative IMRT for HNSCC: effect of different GTV to high-dose CTV margins. Radiother Oncol 2018;126:48–55.
[31] Lee J, Lin JB, Chang CL, et al. Impact of para-aortic recurrence risk-guided intensity-modulated radiotherapy in locally advanced cervical cancer with positive pelvic lymph nodes. Gynecol Oncol 2018;148:291–8.
[32] Viallard C, Larrivee B. Tumor angiogenesis and vascular normalization: alternative therapeutic targets. Angiogenesis 2017;20:409–26.
[33] Minion LE, Tewari KS. Cervical cancer—State of the science: from angiogenesis blockade to checkpoint inhibition. Gynecol Oncol 2018;148:609–21.
[34] Monk BJ, Sill MW, Burger RA, et al. Phase II trial of bevacizumab in the treatment of persistent or recurrent squamous cell carcinoma of the cervix: a gynecologic oncology group study. J Clin Oncol 2009;27:1069–74.
[35] Plassender KS, Liu MC, Tewari KS. Bevacizumab in cervical cancer: 5 years after. Cancer J 2018;24:187–92.
[36] Yang L, Xu Y, Luo P, et al. Baseline platelet counts and derived inflammatory biomarkers: prognostic relevance in metastatic melanoma patients receiving Endostar plus dacarbazine and cisplatin. Cancer Manag Res 2019;11:3681–90.
[37] An J, Lv W, Endostar (rh-endostatin) versus placebo in combination with vinorelbine plus cisplatin chemotherapy regimen in treatment of advanced non-small cell lung cancer: a meta-analysis. Thorac Cancer 2018;9:606–12.