Palliative chemotherapy in recurrent carcinoma cervix: experience from a regional cancer centre in southern India

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Aims: To evaluate the clinical outcome and complications with two different palliative chemotherapy regimens in recurrent cervical carcinoma.

Methods and materials: Forty (40) women with recurrent cervical squamous cell carcinoma were treated with palliative chemotherapy using paclitaxel plus cisplatin or single-agent docetaxel. Clinical outcome and toxicities were analysed. The parameters in two arms were compared using Student’s t-test and statistical analysis was done using R software.

Results: At a median follow up of 1.35 years the clinical outcome was complete response/partial response in 50% and 60% and progressive disease in 20% and 10% of the patients with either paclitaxel/cisplatin or docetaxel, respectively, which was not statistically significant. Stable disease (SD) was 30% in both arms. Toxicity included nausea, seen in all the patients in both arms, and diarrhoea, seen in 90% and 70% of the patients in the two arms, respectively. Grade II to III neutropenia was seen in 10% of patients with paclitaxel/cisplatin and none with docetaxel. Hypersensitivity was encountered in 40% and 30% in the two arms, respectively.

Conclusion: There was no significant difference in clinical outcome and morbidity in patients with either paclitaxel/cisplatin or single-agent docetaxel. Further prospective clinical trials with larger study groups and longer follow-up are required to substantiate these claims.

Keywords: docetaxel, paclitaxel/cisplatin, palliative chemotherapy, recurrent cervical cancer

Introduction
Cervical cancer is one of the common cancers seen in developing countries worldwide. It is also the most common cancer in women presenting at Kidwai Memorial Institute of Oncology, Bangalore, India, where this study was conducted. Notwithstanding the fact that it is curable if detectable at an early stage a considerable number of cases do recur in spite of adequate treatment. Palliative chemotherapy is offered to patients who develop local regional recurrence and the outcomes of this are variable.

There is a paucity of data with regard to the optimal palliative chemotherapy regimen in such cases.

Most of the studies reported in the literature are either case series, have a small sample size or are controversial.1–22

Against this background, we embarked on a retrospective study to identify the optimal regimen with regard to clinical outcome and toxicity between two chemotherapy schedules commonly used at our institute, i.e. paclitaxel with cisplatin or single-agent docetaxel.

Methods and materials
This was a retrospective study conducted at Kidwai Memorial Institute of Oncology (KMIO), Bangalore. The study population comprised 40 patients with recurrent squamous cell carcinoma of the cervix, who were treated with palliative chemotherapy. The two common regimens of chemotherapy used in first-line salvage setting at our institute were paclitaxel plus platinum (cisplatin) or single agent docetaxel. All the patients received six cycles of either of the above regimens. The decision for a chemotherapy regimen was based on issues like affordability, insurance coverage and tolerability.

Baseline parameters such as age, performance score (KPS), ‘T’ size, nodal status, HPV status and histopathological grading of tumours (Table 1) were comparable between the two groups.

Clinical features
All the patients in the present study had a history of white discharge per vagina. Other symptoms like bleeding per vagina and low back pain were occasionally noted.

All the patients in the present study had a good performance score. General physical examination was essentially normal in all patients.

Chemotherapy
Informed consent was taken from all patients. Baseline CT scan of abdomen and pelvis, CBC, LFT, RFT, HIV/HBsAg, and histopathological report were collected.

Twenty patients each received paclitaxel+cisplatin and docetaxel respectively. Response was evaluated using clinical examination findings and CT scan findings after completion of six cycles of chemotherapy using RECIST criteria.

A toxicity profile was assessed during and after chemotherapy. After completion of chemotherapy, patients were reviewed every month during the first three months of follow-up, once in
two months during the next six months and once in three months thereafter.

Response and toxicity were documented at each visit. Results were tabulated and analysed using Student’s t-test using R software (https://www.r-project.org/).

**Paclitaxel+cisplatin (arm A)**
Paclitaxel 175 mg/m² was administered in normal saline using a glass bottle and codon set over three hours, after premedication with diphenhydramine, a 5HT3 inhibitor, corticosteroids and an H2 receptor blocker.

Cisplatin 100 mg/m² was administered in normal saline over three hours with adequate hydration and electrolyte supplementation, following paclitaxel.

Oral steroids, an H2 receptor blocker and a 5HT3 blocker were advised for three days following chemotherapy. The above combination was repeated every 21 days. CBC, LFT, RFT and electrolytes were done prior to each cycle.

**Docetaxel (arm B)**
Docetaxel 120 mg/m² was administered in normal saline using a glass bottle and codon set over two hours, after premedication with diphenhydramine, a 5HT3 inhibitor, corticosteroids and an H2 receptor blocker.

Oral steroids, an H2 receptor blocker and a 5HT3 blocker were advised for three days following chemotherapy. The above combination was repeated every 21 days. CBC, LFT, RFT and electrolytes were done prior to each cycle.

**Results**
At a median follow-up duration of 1.4 years in arm A and 1.3 years in arm B response to chemotherapy was analysed and was found to be complete response (CR) or partial response (PR) in 50% and 60% of patients, progressive disease (PD) in 20% and 10% of patients in arm A and arm B, respectively, which was not significantly different; 30% of patients in each arm had Stable disease (SD). Two patients in arm A and none in arm B had CR (Table 2).
Toxicity profile

All patients were reviewed during chemotherapy and toxicity was documented at each visit. Nausea was seen in 100% of patients in both arms of the study. Two cases of neutropenia were seen in arm A. Diarrhoea was seen in 25% and 10% respectively. Hypersensitivity was seen in 40% and 30% of patients in arm A and arm B, respectively (Table 3).

Discussion

Carcinoma of the uterine cervix is currently the commonest malignancy affecting women in India. Worldwide, chemotherapy has been used in recurrent cervical carcinoma with variable results. At present, cisplatin in combination with paclitaxel is the standard-of-care chemotherapy in the palliative management of cervical cancer.

The combination of paclitaxel with cisplatin was evaluated in a phase II study by the Gynecologic Oncology Group (GOG) and was found to be highly active in recurrent squamous cell carcinoma of the cervix with an overall response rate of 46.3%. Paclitaxel was given at a dose of 135 to 170 mg/m² as a 24-hour infusion along with cisplatin 75 mg/m² over three hours. Myelosuppression was the dose limiting toxicity.

The combination of paclitaxel with cisplatin was found to be superior to cisplatin alone with respect to response rate and progression-free survival in 280 patients in a phase III trial by GOG. The dose of cisplatin was 50 mg/m² and paclitaxel 135 mg/m² administered every 21 days for six cycles.

Single-agent docetaxel at 100 mg/m² once in 21 days was found to have minimal activity in refractory squamous cell cancer of the cervix in a GOG phase II study with 8.7% partial response, 34.8% stable disease and 39% progressive disease. Myelosuppression, infection, gastrointestinal toxicity and constitutional effects were commonly seen.

A small phase II study evaluated weekly docetaxel at 35 mg/m², which showed only limited activity in recurrent squamous cell cancer of the cervix. With a median of two cycles, there were no objective responses to chemotherapy.

Against this background, we retrospectively studied the role of a paclitaxel/cisplatin combination versus single-agent docetaxel chemotherapy in recurrent squamous cell carcinoma of the cervix.

We analysed 20 cases in each arm. The two arms were well matched with regard to age, performance, HPV status, nodal status and histological grade. At a median follow-up duration of 1.3 years, the overall response rate was 50% with paclitaxel/cisplatin and 60% with docetaxel. Progressive disease was seen in 20% and 10% of patients in arm A and arm B, respectively; 30% of patients in each arm had stable disease.

The excellent results seen in our study compared with the published literature could be attributed to the fact that all the patients completed six cycles of the planned chemotherapy and the higher dose of chemotherapy: paclitaxel (175 mg/m²), cisplatin (100 mg/m²) and docetaxel (120 mg/m²).

Neutropenia, diarrhea, nausea and hypersensitivity were the common toxicities associated with chemotherapy in both arms of the study.

Conclusion

We conclude that, in our series of 40 patients with recurrent cervical cancer treated with palliative chemotherapy, there was no difference in clinical outcome and complication rates with either paclitaxel/cisplatin or single-agent docetaxel.

Prospective studies with a larger sample size and longer follow-up are warranted in the future.

References

1. Rose PG, Blessing JA, Gershenson DM, et al. Paclitaxel and cisplatin as first-line therapy in recurrent or advanced squamous cell carcinoma of the cervix: a gynecologic oncology group study. J Clin Oncol. 1999 Sep;17(9):2676–80.
2. Moore DH, Blessing JA, McQuelon RP, et al. Phase III study of cisplatin with or without paclitaxel in stage IVB, recurrent, or persistent squamous cell carcinoma of the cervix: a gynecologic oncology group study. J Clin Oncol. 2004 Aug 1;22(15):3113–9.
3. Garcia AA, Blessing JA, Vaccarella L. Phase II clinical trial of docetaxel in refractory squamous cell carcinoma of the cervix. Am J Clin Oncol. 2007;30(4):428–31.
4. Pearl ML, Johnston CM, McMeekin DS. A phase II study of weekly docetaxel for patients with advanced or recurrent cancer of the cervix. Gynecol Obstet Invest. 2007;64(4):193–8. Epub 2007 Jul 30.
5. Nguyen HN, Nordqvist SR. Chemotherapy of advanced and recurrent cervical carcinoma. Semin Surg Oncol. 1999 Apr–May;16(3):247–50.
6. Sugiyama T, Yakuishi M, Noda K, et al. Phase II study of irinotecan and cisplatin as first-line chemotherapy in advanced or recurrent cervical cancer. Oncology. 2000;58(1):31–7.
7. Fiorica J, Holloway R, Ndubisi B, et al. Phase II trial of topotecan and cisplatin in persistent or recurrent squamous and nonsquamous carcinomas of the cervix. Gynecol Oncol. 2002 Apr;85(1):89–94.
8. Tiersten AD, Selleck MJ, Hershman DL, et al. Phase II study of topotecan and paclitaxel for recurrent, persistent, or metastatic cervical carcinoma. Gynecol Oncol. 2004 Feb;92(2):635–8.
9. Tambaro R, Scambia G, Di Maio M, et al. The role of chemotherapy in locally advanced, metastatic and recurrent cervical cancer. Crit Rev Oncol Hematol. 2004 Oct;52(1):33–44.
10. Cadron I, Van Gorp T, Amanat F, et al. Chemotherapy for recurrent cervical cancer. Gynecol Oncol. 2007 Oct;107(1):S113–S118. Epub 2007 Sep 4.
11. Moore DH. Chemotherapy for advanced, recurrent, and metastatic cervical cancer. J Natl Compr Canc Netw. 2008 Jan;6(1):S3–7.
12. Tao X, Hu W, Ramirez PT, et al. Chemotherapy for recurrent and metastatic cervical cancer. Gynecol Oncol. 2008 Sep;110(3 Suppl 2):S67–S71. doi: 10.1016/j.ygyno.2008.04.024. Epub 2008 Jun 3.
13. Pectasides D, Kampisioras K, Papaxoinis G, et al. Chemotherapy for recurrent cervical cancer. Cancer Treat Rev. 2008 Nov;34(7):603–13. doi: 10.1016/j.ctrv.2008.05.006. Epub 2008 Jul 26.
14. Gadducci A, Tana R, Cosio S, et al. Treatment options in recurrent cervical cancer (Review). Oncol Lett. 2010 Jan;1(1):3–11. Epub 2010 Jan 1.
15. Puls LE, Phillips B, Schammel C, et al. A phase II trial of weekly topotecan in the treatment of recurrent cervical carcinoma. Med Oncol. 2010 Jun;27(2):368–372. doi: 10.1007/s12032-009-9219-7. Epub 2009 Apr 21.
16. Lorusso D, Pietragalla A, Mainenti S, et al. Review role of topotecan in gynaecological cancers: current indications and perspectives. Crit Rev Oncol Hematol. 2010 Jun;74(3):163–74. doi: 10.1016/j.critrevonc.2009.08.001. Epub 2009 Sep 18.
17. Lee YY, Lee JW, Park HS, et al. Sequence-dependent hematologic side effects of topotecan and cisplatin in persistent or recurrent cervical cancer. Gynecol Oncol. 2010 Oct;119(1):87–91. doi: 10.1016/j.ygyno.2010.05.030. Epub 2010 Jun 26.
18. Kurtz JE, Freyer G, Joly F, et al. Combined oral topotecan plus carboplatin in relapsed or advanced cervical cancer: GINECO phase II–III trial. Anticancer Res. 2012 Mar;32(3):1045–9.
19. Kimura T, Miyatake T, Ueda Y, et al. Cervical non-squamous carcinoma: an effective combination chemotherapy of taxane, anthracycline and platinum for advanced or recurrent cases. Eur J Obstet Gynecol Obstet Gynecol. 2010.05.030. Epub 2010 Jun 26.
Reprod Biol. 2012;164(2):200–04. doi: 10.1016/j.ejogrb.2012.06.008. Epub 2012 Jul 4.

20. Leath CA 3rd, Straughn JM Jr. Chemotherapy for advanced and recurrent cervical carcinoma: results from cooperative group trials. Gynecol Oncol. 2013;129(1):251–7. doi: 10.1016/j.ygyno.2012.12.035. Epub 2012 Dec 30.

21. Eskander RN, Tewari KS. Development of bevacizumab in advanced cervical cancer: pharmacodynamic modeling, survival impact and toxicology. Future Oncol. 2015 Mar;11(6): 909–22. doi: 10.2217/ fon.14.276.

22. Krill LS, Tewari KS. Integration of bevacizumab with chemotherapy doublets for advanced cervical cancer. Expert Opin Pharmacother. 2015 Apr;16(5):675–683. doi: 10.1517/14656566.2015.1010511. Epub 2015 Feb 3.

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