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Original Article

Epidemiology and Outcomes with Platinum-Based Chemotherapy in Recurrent or Metastatic Carcinoma Cervix in a Developing Country: Experience from a Tertiary Oncology Centre in Southern India


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Abstract

Introduction: Carcinoma cervix is the leading cause of cancer in Indian women. Recurrent/metastatic cervix is the most aggressive form of the disease. There is paucity of data in this setting in Indian women regarding outcomes with palliative chemotherapy.

Methods: We retrospectively analyzed hospital registry data between January 2013 and December 2014 for recurrent/metastatic carcinoma cervix patients who were planned for palliative chemotherapy and assessed their demographic parameters, response and survival outcomes with chemotherapy.

Results: We identified 165 cases of recurrent/metastatic carcinoma cervix. Median age at presentation was 48 years. Most common symptoms at presentation were bleeding or white discharge per vagina and lower abdominal pain. Majority of the patients were multiparous. Histologically squamous cell carcinoma was found most commonly (93.3%) with adenocarcinoma and adenosquamous carcinoma being exceedingly uncommon (3.63% each). 38% of patients were upfront metastatic while rest were recurrent disease. Most common sites of metastasis were retroperitoneal lymph nodes (21.21%), liver (11.51%), lung (9.69%), supraclavicular lymph nodes (8.48%) and bone (7.27%). After a median of 6 cycles of paclitaxel and carboplatin based chemotherapy, overall response rate (ORR) was 26.7% with 10.5% complete remission (CR) and 16.4% partial remission (PR) rates. Median progression free survival (PFS) was 6 months while median overall survival (OS) was 11 months.

Conclusion: Recurrent/metastatic cervical carcinoma is an aggressive disease. Our patients showed an ORR of 26.7% to palliative chemotherapy with median PFS of 6 months and median OS of 11 months. Further research is required related to novel targeted agents and non-platinum doublets.

Keywords: Recurrent/metastatic cervical carcinoma, Paclitaxel/Platinum chemotherapy, Indian population

Introduction

Carcinoma cervix is the fourth most common cause of cancer in females worldwide with an estimated 528,000 new cases per year where about one fifth of this total are registered from India (1). While population based cancer registries in India show declining trend in incidence, it still remains a leading cause of cancer in Indian women. Every year 122,844 women are diagnosed with cervical cancer and 67,477 die from the disease in India (2).

Depending on the stage of presentation, up to 15–60% of cases develop recurrent or metastatic disease after primary treatment with surgery or radiotherapy during their lifetime; this constitutes as a major cause of mortality related to the disease (3). A study by Quinn and his colleagues reported 1 year overall survival rates of 42% for metastatic disease, which is only 10% at 5 years (4). Many studies over the years have attempted to improve outcomes in these patients with various chemotherapeutic regimens.

There is little data on the demographic profile of Indian patients with recurrent or metastatic disease...
and their outcomes to chemotherapy. Here we analyzed our patients with respect to conventional paclitaxel and platinum combination chemotherapy related outcomes.

**Methods**

We retrospectively analyzed data from hospital registry from January 2013 to December 2014 for recurrent or metastatic carcinoma cervix patients who were planned for platinum--based palliative chemotherapy. Identified patients were analyzed with respect to patient profile including risk factors related to disease; disease symptoms and duration of the same; baseline disease stage and histology as well as prior treatment received. Analysis of treatment factors including total number of chemotherapy cycles received and response rates were assessed. Survival analysis was performed by Kaplan Meier method using Statistical Package for Social Sciences 20 (SPSS Inc., 233 South Wacker Drive, 11th floor, Chicago). To compare prognostic factors including site of recurrence and time of recurrence post therapy, log rank test was used.

**Results**

We identified a total of 165 patients with recurrent or metastatic carcinoma cervix who were planned for palliative chemotherapy. 53.93% (n=89) of cases were metastatic while 48.48% (n=80) were local recurrences. Out of metastatic diseases 38.2% (n=34) were upfront metastatic.

Median age of presentation was 48 years (range 27 to 76 years). 87.87% (n=145) of patients were multipara out of which 19% (n=31) were grand multipara, defined as women with more than 4 live births. Median age at first child birth was 21 years with 85% (n=140) had first child birth before 25 years of age.

Most common presenting symptoms were bleeding per vagina (70.9%, n=117), white discharge per vagina (64.24%, n=106) and abdominal pain (37.57%, n=62). Median symptom duration prior to reporting to the hospital was 6 months.

For recurrent cases, stage at first presentation was I (18%, n=30), II (36%, n=60), III (25%, n=41) and IVA (2.4%, n=4) in our series. 80% (n=108) had received prior Radiotherapy (RT), out of which 76.85% (n=83) had received concurrent chemotherapy; 20% (n=27) had undergone surgery. These patients had a median time to progression of 18 months (range 3 –192 months) with 45.19% (n=61) relapsed within 1 year, 31.85% (n=43) between 1 to 2 years, 6.67% (n=9) between 2 to 3 years, 8.89% (n=12) between 3 to 5 years and 8.15% (n=11) relapsed beyond 5 years of primary therapy. The most common sites of metastasis in decreasing order of frequency were retroperitoneal lymph nodes (21.21%), liver (11.51%), lung (9.69%), supraclavicular lymph nodes (8.48%) and bone (7.27%). 32.6% (n=29) metastatic cases had multiple sites of metastasis. Table 1 describes all the sites of metastasis that were identified.

Tumour histology identified in our study is described in Table 2. Most common histology found was squamous cell carcinoma (SCC) in 93.3% (n=154) of cases.

All the patients were planned for palliative chemotherapy with paclitaxel 175mg/m² and carboplatin AUC5 on day 1 every 21 days for 6 cycles as the institutional protocol. However only 54% (n=89) of patients could complete all 6 cycles of planned course of chemotherapy. Of the rest, 8.48% (n=14) had stopped chemotherapy before 6 cycles due to toxicity, 23% (n=38) experienced progressive disease or death on treatment before 6 cycles and 14.5% (n=24) were lost to follow up early during treatment.

Objective response rate at a median of 6 chemotherapy cycles (range 0 to 6) was 26.7% (n=44), including 10.3% (n=17) complete response (CR) and 16.4% (n=27) partial response (PR). 23.6% (n=39) patients had stable disease.
(SD) while 32.7% (n=54) developed progressive disease (PD). Median progression free survival (PFS) was 6 months while median overall survival (OS) was 11 months (Figure 1).

While analyzing outcomes with reference to recurrent disease, we identified significant difference in PFS (p=0.006), but not in OS (p=0.098) between the groups with locoregional recurrence versus distant recurrence (Figure 2). Cases with recurrence within first year of primary therapy had significantly lower PFS (p=0.005) and OS (p=0.007) than the ones with delayed relapses (Figure 3).

**Discussion**

Carcinoma cervix is the most common gynecological malignancy in Indian women with preponderance in rural population. However, there are many challenges faced regarding prevention, diagnosis and management of this disease. Indian Council of Medical Research initiated a network of cancer registries under the National Cancer Registration Programme in 1981 and data collection which began since 1982 has shown variations in regional incidence and mortality across the country, especially in rural versus urban areas. The reasons of such variations may be multifactorial. There is no well-planned nationwide
screening program for cervical cancer and routine HPV vaccination for prevention is not followed. There are many discrepancies in treatment as well. Due to lack of education and awareness, many of these females present to healthcare facility late during the course of illness. In our study we found median duration of symptoms before approaching a health care facility of 6 months. Also many of the patients are lost to follow up early during the course of treatment due to socioeconomic factors which is an important hindrance in treatment of such cases which in our study was 14.5%. Our centre caters to a population mainly from Karnataka and nearby states in southern India. Our study tried to focus on the advanced disease which is the main cause of mortality by cervical carcinoma in our population.

Major risk factors for the disease leading to high risk of Human Papilloma Virus (HPV) infection include early initiation of sexual activity, multiple sexual partners, early age of first childbirth, increasing number of parity, h/o sexually transmitted diseases and immunocompromised state. Majority of the study population was multiparous (87.87%) with 19% women being grand multipara. Majority of the patients had less than 24 years of age at first child birth. Berrington de González et al also have shown Relative Risk (RR) of 1.5 for >=3 full term pregnancies, and 2.05 for grand multipara. They also showed RR of 1.66 for first child birth at less than 25 years of age which increases to 2.16 for those with less than 20 years and 2.72 for less than 17 years of age at their first child birth.

For local recurrences, up to 75% of cases will be symptomatic with most common symptoms being serosanguinous vaginal discharge, abdominal pain and when pelvic sidewalls are involved a characteristic triad of pain, leg edema and hydronephrosis. However asymptomatic recurrences can be found in patients while on surveillance post therapy. Disease presenting only as distant metastasis mostly present with nonspecific symptoms including weight loss, malaise and according to sites of metastasis may also present with cough, hemoptysis, upper abdominal discomfort or neck swelling. Thus role of PET scanning in identifying distal metastasis remains important before considering aggressive local salvage therapy for suspected locoregional only recurrences.

Our series suggested median duration of recurrence of 18 months post primary treatment which is consistent with the available literature. However occasional recurrences may occur even after 5 years of therapy, the incidence of which in our study was found to be 8.15%. Thus continuous surveillance of these patients post treatment is warranted.

Recurrence rates, both local and distant, vary according to presenting stage. Reported local recurrences are 10% for stage IB, 15% for stage IIA, 25% for stage IIB, 40% for stage III and up to 75% for stage IVA. Carlson et al have published their data from MDACC showing frequency of distant metastasis at 0.74% in stage IA, 4.74% at stage IB, 9.21% at stage IIA, 16.18% at stage IIB, 20.38% at stage IIIA, 20.71% at stage IIIB and 24.13% at stage IVA disease.

We found that the most common site of recurrence is at retroperitoneal lymph nodes followed by liver, lung,
supraclavicular lymph nodes and bones. Carlson’s series suggested common sites of metastasis being lung, mediastinal lymph nodes, supraclavicular lymph nodes, bones and liver (9). Fulcher et al reported cases of recurrent cervical cancer with metastasis to Pelvic or para-aortic nodes (75 and 62 percent, respectively), Lung (33 to 38 percent), Liver (33 percent), Peritoneum (5 to 27 percent), Adrenal gland (14 to 16 percent), Intestines (12 percent) and Skin (10 percent) (10).

Squamous cell carcinoma is the most common histology of cervical carcinoma, however other histologies are also found on which adenocarcinoma predominates (11). In our population we found excess of SCC grade 2 histology while grade 3 tumours were less common. Adenocarcinoma histology accounts for about 20–25% of cases of cervical cancer in western literature out of which 20–30% are adenosquamous histology, these histologies were found in only 3.6% each in our series (12). Adenocarcinoma is considered relatively radio-resistant subtype and outcomes are better with surgery than with radiotherapy in early stage disease including risk of relapse; however some studies argue against this notion (13) and prognostic significance of these histologies remains controversial. Nakanishi et al showed significantly worse prognosis when lymph node metastasis was seen in early stage adenocarcinoma as compared to squamous histology, while majority of evidence suggests no impact on survival irrespective of stage (14,15). Similarly a study by Dos Reis from MD Anderson Cancer Centre in early stage adenosquamous carcinoma revealed shorter time of recurrence as compared to adenocarcinoma without significant effect on recurrence free survival or overall survival (16).

Various chemotherapeutic agents have been tried in metastatic cervical carcinoma over the years with single agent responses ranging from 10–35% as reported in various series (Table 3). Cisplatin remains the most active agent in recurrent or metastatic disease with overall response duration ranging from 4 to 6 months with overall survival of disappointing 7 months (17). Initial studies attempted to assess the effect of increased dose of the drug, and suggested that a dose of 100mg/ m² improved ORR over 50mg/m², without significantly affecting PFS or OS and with increased toxicity at higher doses (18). Later attempts were made to combine cisplatin with another agent in order to improve survival outcomes. Various trials in this regard proved the benefits of platinum doublets which has now become the standard of care. Recommended platinum based doublets include paclitaxel, gemcitabine, topotecan or vinorelbine (19–21). Responses recorded usually are better for recurrences in non–irradiated areas. Recently after a systematic review of all randomized trials, Hirte HW et al have also published clinical practice guidelines for management of recurrent, metastatic cervical carcinoma (22). Carboplatin is considered non–inferior to cisplatin as far as efficacy is concerned and is better tolerated in metastatic setting according to results from a Japanese study (23). Platinum triplet showed a significant improvement in response rates of up to 69% in a phase II study by Buxton et al, however larger Gynecologic Oncology Group study (GOG) study failed to show any benefit as compared to doublets and thus three drug combinations are not recommended in clinical practice (24,25). Recent GOG study has also highlighted overall survival benefit with the use of targeted therapy with angiogenesis inhibitor monoclonal antibody bevacizumab (26). Our institutional protocol follow paclitaxel and carboplatin doublet as the first line chemotherapy for recurrent or metastatic setting. Affordability remains an important issue before offering novel monoclonal antibodies to our patients.

Table 3. Response Rates to single agent chemotherapy in palliative setting
With a median of 6 cycles of chemotherapy ORR was 26.7% with median PFS of 6 months and a median OS of 11 months in our patients. Outcomes with paclitaxel and platinum based chemotherapy in major trials are summarized in Table 4. We also identified a negative impact of distant recurrence and delayed recurrence beyond 1 year of primary therapy on PFS. While OS was influenced by time of recurrence, it was not affected significantly by site of recurrence.

We would also like to acknowledge the fact that there is a significant increase in the number of patients receiving platinum in first line setting concurrently with radiotherapy, 47.87% of our patients had received cisplatin or carboplatin concurrently with radiotherapy as primary treatment. This makes it imperative to find novel active non–platinum doublets in order to achieve better outcomes in these patients, recent GOG study has provided us with one such option of paclitaxel and topotecan combination (26).

### Table 4. Outcomes with paclitaxel and platinum based chemotherapy in major trials

<table>
<thead>
<tr>
<th>STUDY</th>
<th>Paclitaxel + Platinum Arm</th>
<th>N</th>
<th>CR (%)</th>
<th>PR (%)</th>
<th>SD (%)</th>
<th>PFS (months)</th>
<th>OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOG 169 (Moore DH et al 2004)</td>
<td>Cisplatin 50mg/m2 + Paclitaxel 135mg/m2 q3w</td>
<td>130</td>
<td>15</td>
<td>21</td>
<td>-</td>
<td>4.8</td>
<td>9.7</td>
</tr>
<tr>
<td>GOG 204 (Monk BJ et al. 2009)</td>
<td>Cisplatin 50mg/m2 + Paclitaxel 135mg/m2 q3w</td>
<td>118</td>
<td>2.9</td>
<td>26.2</td>
<td>48.4</td>
<td>5.82</td>
<td>12.87</td>
</tr>
<tr>
<td>GOG 240 (Tewari KS et al. 2014)</td>
<td>Cisplatin 50mg/m2 + Paclitaxel 135mg/m2 over 24 hours or 175mg/m2 over 3 hours q3w</td>
<td>114</td>
<td>7.9</td>
<td>31</td>
<td>-</td>
<td>7.6</td>
<td>14.3</td>
</tr>
<tr>
<td>JCOG0505 (Kitagawa R et al. 2015)</td>
<td>Cisplatin 50mg/m2 + Paclitaxel 135mg/m2 q3w (TP)</td>
<td>127 (TP)</td>
<td>3.9 (TP)</td>
<td>54.9 (TP)</td>
<td>-</td>
<td>6.9(TP)</td>
<td>18.3 (TP)</td>
</tr>
<tr>
<td></td>
<td>OR Carboxiplatin AUC 5 + Paclitaxel 175mg/m2 q3w (TC)</td>
<td>126 (TC)</td>
<td>7.1 (TC)</td>
<td>55.5 (TC)</td>
<td>-</td>
<td>6.2(TC)</td>
<td>17.5 (TC)</td>
</tr>
<tr>
<td>Present study</td>
<td>Carboxiplatin AUC 5 + Paclitaxel 175mg/m2</td>
<td>165</td>
<td>10.3</td>
<td>16.4</td>
<td>23.6</td>
<td>6</td>
<td>11</td>
</tr>
</tbody>
</table>

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### Conclusion

Recurrent or metastatic cervical carcinoma is an aggressive disease occurring in females with poor outcomes. We report our experience in these patients with their demographic profile. Our patients showed an Objective Response Rate of 26.7% to paclitaxel and carboplatin combination chemotherapy with median PFS of 6 months and median OS of 11 months. Further research is required for improving outcomes of this aggressive entity including novel targeted therapy and non–platinum combination chemotherapy.


