Integrating Chemotherapy in the Management of Cervical Cancer: A Critical Appraisal

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\textbf{Key Words}
Cervix cancer · Neo-adjuvant chemotherapy · Adjuvant chemotherapy · Concurrent chemoradiation · Targeted therapy · Bevacizumab

\textbf{Abstract}
The management of locally advanced cervix cancer has undergone a paradigm shift during the last decade. Concurrent chemoradiation (CCRT) (with cisplatin alone or in combination) is currently the standard treatment approach. CCRT results in a 5-year overall survival rate of 66\% and a disease-free survival of 58\%. About 30–40\% of patients with locally advanced cervical cancer fail to achieve complete response to CCRT; alternative approaches are needed to improve the outcome for such patients. Weekly paclitaxel and carboplatin for 4–6 weeks as dose-dense chemotherapy prior to CCRT could be one such potential approach. The role of adjuvant chemotherapy after CCRT in patients with positive lymph nodes, larger tumor volume and stage III–IVA disease needs further exploration. Adjuvant chemotherapy is also being investigated for early-stage (stages IA2, IB1 or IIA) cervical cancer with presence of risk factors such as lymph node metastasis, lymphovascular space invasion and invasion depth of more than 10 mm, microscopic parametrial invasion, non-squamous histology and positive surgical margins. For patients with early-stage disease (IA2–IIA), short-course chemotherapy prior to surgery is associated with an improved outcome in many studies. Neo-adjuvant chemotherapy followed by fertility preservation surgery is feasible in carefully selected young patients with bulky stage IB1 disease. Recently, a number of molecular pathways have been identified as potential therapeutic targets. Bevacizumab – an inhibitor of vascular endothelial growth factor – is associated with improved survival in patients with recurrent/metastatic cervical cancer. Whether bevacizumab and other similar novel agents targeting molecular pathways could be used in front-line treatment along with cytotoxic chemotherapy is likely to be an area of research in future studies.
features distinct from those seen in industrialized nations: young age at diagnosis (median age 35–38 vs. 50–58 years), higher frequency of squamous histology (>90 vs. ≤80%) and presence of locally advanced stage (stage IIB–IVA) in >80% of women with a higher disease volume compared to ≤50% [2].

The outcome for early-stage cervical cancer is generally good: the 5-year survival rates for locally advanced disease vary from 50 to 65% for stage II B, from 28 to 35% for stage IIIB and from 5 to 15% for stage IVA disease. Thus, 30–50% of patients develop treatment failure; locoregional recurrence is the main cause of failure. The presence of a large primary tumor (larger tumors tend to have hypoxic foci which are relatively radio-resistant) and/or pelvic/para-aortic lymph nodes (harboring metastatic disease) are possible contributing factors [3]. Chemotherapy was initially introduced for the treatment of recurrent/metastatic cervix cancer and has subsequently been explored in primary treatment either as neo-adjuvant prior to radiation or surgery or as adjuvant after radiation or surgery (table 1). Currently, chemotherapy administered concurrently with radiation therapy (concurrent chemoradiation, CCRT) is the standard treatment for locally advanced cervical cancer. We have made an attempt to review the role of chemotherapy in the management of cervical cancer.

**Palliative Chemotherapy**

The role of cisplatin as an active agent in the treatment of recurrent cervix cancer was established in late 1980s. Other active agents include ifosfamide, bleomycin, 5-fluorouracil, mitomycin C, paclitaxel, gemcitabine, topotecan, etc. (table 2). A number of combinations, e.g. bleomycin, ifosfamide and cisplatin (BIP), cisplatin and 5-fluorouracil, have been used in the past [4]. In the past decade, the role of combinations based on paclitaxel plus cisplatin/carboplatin has been explored, with achievement of complete response (CR) in 10–20% of patients and a median duration of response of 7–12 months [3–6]. Though combination chemotherapy produced higher response rates, overall survival was not significantly different compared to cisplatin alone in one study from our center [6]. In a Gynecologic Oncology Group (GOG) study, addition of paclitaxel to cisplatin led to an increased response rate (from 19 to 36%), median progression-free survival (from 2.8 to 4.8 months) and overall survival (from 8.8 to 9.7 months) [7]. Monk et al. [8], for

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**Table 1. Advantages and disadvantages of various chemotherapy schedules**

<table>
<thead>
<tr>
<th>Schedule</th>
<th>Advantage</th>
<th>Disadvantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>NACT</td>
<td>Elimination of micrometastases</td>
<td>May select out therapy-resistant clone</td>
</tr>
<tr>
<td></td>
<td>Shrinkage of the primary tumor bulk to achieve operability</td>
<td>Delay in definitive therapy – RT</td>
</tr>
<tr>
<td>Concurrent therapy</td>
<td>CT has cytotoxic and anti-proliferative effects</td>
<td>Increased toxicity</td>
</tr>
<tr>
<td></td>
<td>CT also targets microscopic systemic foci</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CT inhibits the repair of sublethal damage from radiation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CT also has radio-sensitizer and hypoxia-sensitizer effects in a large primary tumor</td>
<td></td>
</tr>
<tr>
<td>Adjuvant therapy</td>
<td>Eradicates residual/microscopic disease</td>
<td>Increased toxicity</td>
</tr>
</tbody>
</table>

Adapted from [2]. CT = Chemotherapy.

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**Table 2. Response rates to various chemotherapeutic agents in advanced or recurrent cervical cancer**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Patients, n</th>
<th>Objective RR, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin 50 mg/m² (day 1)</td>
<td>497</td>
<td>20</td>
</tr>
<tr>
<td>Cisplatin 100 mg/m² (day 1)</td>
<td>497</td>
<td>31.4</td>
</tr>
<tr>
<td>Cisplatin 20 mg/m² (days 1 – 5)</td>
<td>497</td>
<td>25</td>
</tr>
<tr>
<td>Carboptatin</td>
<td>175</td>
<td>15</td>
</tr>
<tr>
<td>5FU</td>
<td>142</td>
<td>20</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>96</td>
<td>18</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>56</td>
<td>15.7</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>74</td>
<td>19</td>
</tr>
<tr>
<td>Cisplatin plus vinorelbine</td>
<td>73</td>
<td>30</td>
</tr>
<tr>
<td>Cisplatin plus topotecan</td>
<td>147</td>
<td>27</td>
</tr>
<tr>
<td>BIP</td>
<td>141</td>
<td>31.2</td>
</tr>
<tr>
<td>TIP</td>
<td>45</td>
<td>67</td>
</tr>
</tbody>
</table>

Adapted from [4]. RR = Response rate; BIP = bleomycin, ifosfamide and cisplatin; TIP = paclitaxel, ifosfamide and cisplatin; 5FU = 5-fluorouracil.
the Gynecologic Oncology Group (GOG), reported results of a randomized study comparing the results of four doublets in 513 patients with recurrent or persistent disease. There was no difference in overall survival in four doublets: paclitaxel-cisplatin versus gemcitabine, cisplatin versus vinorelbine, cisplatin versus topotecan plus cisplatin. However, there was a trend favoring paclitaxel-cisplatin with regard to response rate, progression-free survival and overall survival [8].

Lower response rates in patients with recurrent cervical cancer are due to compromised blood flow in the affected area following irradiation, thus reducing the local concentration of chemotherapeutic drugs. Patients with extra-pelvic recurrence (un-irradiated site, e.g. pulmonary metastasis) have a better outcome than those with pelvic disease. In some cases, responses can be durable [6]. Toxicity to chemotherapy is moderate. Patients with a poor performance status (ECOG 3–4), hydronephrosis and hypoalbuminemia are poor candidates for chemotherapy.

More recently, Kitagawa et al. [9] have reported results of a Japanese Gynecologic Oncology Group (JGOG) study. In this non-inferiority study, the authors compared carboplatin plus paclitaxel (TC) with cisplatin plus paclitaxel (TP) in metastatic or recurrent cervical cancer. Complete and partial response rates were similar: 58.8% (95% CI 48.6–68.5) in the TP group and 62.6% (95% CI 52.3–72.2) in the TC group (p = 0.665). The toxicity profile was different in both arms: incidence of grade 4 neutropenia (75 vs. 45.2%, p < 0.001), grade 3–4 febrile neutropenia (16 vs 7.1%, p < 0.03), creatinine elevation (2.4 vs. 0%, p = 0.12) and nausea/vomiting (6.4 vs. 3.2%, p = 0.25) was higher in the TP group, whereas the incidence of thrombocytopenia (24.6 vs. 3.2%) and sensory neuropathy (4.8 vs. 0%) was higher in the TC group. Overall survival was 17.5 versus 18.5 months in TC group versus TP arm (p = n.s.). The results of this phase III study suggest that paclitaxel and carboplatin may be considered as another standard regimen for treatment of recurrent/metastatic cervical cancer [9].

In a Cochrane database review, Scatchard et al. [10] analyzed 10 randomized trials assessing 1,438 participants. There was no statistically significant difference in response rate between women who received single-agent chemotherapy and those who received combination therapy (response rate 0.94, 95% CI 0.57–1.55). It is important to mention here that many of these trials were conducted between the 1970s and 1990s, had a small number of patients and included inactive agents [10]. At present, there is no data comparing best supportive care with chemotherapy. Data on quality of life following chemotherapy is also limited [10].

**Neo-Adjuvant Chemotherapy**

Between 1990 and 2000, a number of non-randomized and randomized studies explored the use of neo-adjuvant chemotherapy (NACT) prior to radiation in patients with locally advanced cervix cancer (IIB–IVA). The use of primary chemotherapy was based upon the principle that (i) chemotherapy may shrink the primary tumor, making malignant cells sensitive to subsequent radiotherapy (RT), (ii) uncompromised blood flow in radiation-naive patients results in higher chemotherapy drug concentration at tumor site compared to patients pretreated with radiation, and (iii) chemotherapy can eradicate micrometastatic disease. However, delay of definitive treatment, i.e. radiation and selection of resistant clone, are potential disadvantages of NACT [11]. Apart from locally advanced disease, the role of NACT has also been explored in patients with early-stage (IB–IIA) disease prior to surgery or radiation.

**NACT prior to RT**

The results of eight randomized studies are summarized in table 3. Cisplatin-based combinations were used in these studies. Following 2–3 cycles, CR and partial response rates varied from 40 to 80%, with CR in less than 10% of patients [12–20]. However, these studies failed to show an improvement in progression-free and overall survival compared to radiation alone [12–18]. In two studies, the outcome was inferior in the NACT arm [19, 20]. The lack of survival advantage to NACT in the above studies was attributed to lower CR rates to chemotherapy, frequent interruptions in the RT treatment schedule (delay in treatment promoting development of resistant clone) and a small number of patients in each stage (faulty design). The low CR rate was possibly due to the use of a lower dose of cisplatin (50 vs. 75 or 100 mg/m²), 2 cycles of chemotherapy rather than 3 cycles and relatively inactive chemotherapy regimens. The use of 3 cycles of chemotherapy was associated with higher CR rates (22.2% compared to 4.5% with 2 cycles) in a randomized study from our center [21]. From both randomized and non-randomized studies, it is clear that even at a given stage, the patient population is heterogeneous (tumor size <5 cm), bilateral parametrial involvement (complete or less than complete) and presence or absence of lymph node metastasis [12, 21].
Heterogeneity in terms of trial design, drug dose, etc., was further confirmed in a systemic review and meta-analysis of individual patient data (n = 2,074) from 21 randomized trials. Trials using chemotherapy cycle lengths of 14 days and shorter [hazard ratio (HR) = 0.83, 95% CI = 0.69–1.00, p = 0.046] or cisplatin dose intensities greater than or equal to 25 mg/m² per week (HR = 0.91, 95% CI = 0.78–1.05, p = 0.20) tended to show an advantage for NACT on survival. In contrast, trials using cycle lengths longer than 14 days (HR = 1.25, 95% CI = 1.07–1.46, p = 0.005) or cisplatin dose intensities lower than 25 mg/m² per week (HR = 1.35, 95% CI = 1.11–1.14, p = 0.002) tended to show a detrimental effect of NACT on survival [22, 23]. Despite some unexplained heterogeneity, the timing and dose intensity of cisplatin-based NACT appears to have an important impact on a subset of patients. Whether or not it benefits women with locally advanced cervical cancer warrants further exploration [22, 23].

**NACT Followed by Surgery**

Residual disease in almost one third of patients (IIB–IVA) following sequential NACT and RT led investigators to hypothesize that the surgical removal of the remaining tumor mass (thereby removing the resistant clone) may be associated with survival benefit. In the late 1990s, several phase II studies using NACT followed by surgery with or without adjuvant RT reported encouraging results [24, 25]. Subsequently, this issue was addressed in a number of randomized trials (table 4) [26–31] and meta-analyses [32, 33]. Chang et al. [26] randomized 124 patients of stage IB–IIA to receive either 3 cycles of cisplatin, vincristine or bleomycin followed by either hysterectomy (n = 68) or primary pelvic RT (n = 52). The cumulative survival was 81 versus 84% (p = n.s.) at 2 years and 70 versus 61% (p = n.s.) at 5 years in the NACT and RT arms, respectively. There was no significant difference in disease-free survival between the two arms [26]. In a similar study by Benedetti-Panici et al. [27], survival advantage with this strategy was limited to stage IB2–IIB. Most of these studies [23–30] used short-course chemotherapy of 4–6 weeks followed by surgery/RT. Recently, Katsumata et al. [31], for the Japan Clinical Oncology Group, have reported results of a phase III trial. Patients with stage IB2, IIA2 and IIB received 2–4 cycles of the BOMP regimen (bleomycin, vincristine, mitomycin C and cisplatin; BOMP = bleomycin, vincristine, mitomycin C and cisplatin; BOP = bleomycin, vincristine and cisplatin; EpP = epirubicin and cisplatin; MtxCVP = methotrexate, chlorambucil, vincristine and cisplatin; Tattersall et al. [20] 260 EpP 72 92 47 70 0.02

<table>
<thead>
<tr>
<th>Authors [Ref.]</th>
<th>Patients, n</th>
<th>Regime</th>
<th>Response, %</th>
<th>Survival, %</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kumar et al. [12]</td>
<td>184</td>
<td>BIP</td>
<td>70 69</td>
<td>38 43</td>
<td>n.s.</td>
</tr>
<tr>
<td>Tobias et al. [13]</td>
<td>66</td>
<td>BIP</td>
<td>75 56</td>
<td>– –</td>
<td>n.s.</td>
</tr>
<tr>
<td>Leborgne et al. [14]</td>
<td>130</td>
<td>BOP</td>
<td>68 65</td>
<td>38 49</td>
<td>n.s.</td>
</tr>
<tr>
<td>Chauvergne et al. [15]</td>
<td>138</td>
<td>MtxCVP</td>
<td>84.9 88.9</td>
<td>63 60</td>
<td>n.s.</td>
</tr>
<tr>
<td>Cardenas et al. [16]</td>
<td>28</td>
<td>PEPc</td>
<td>5 86</td>
<td>36 50</td>
<td>n.s.</td>
</tr>
<tr>
<td>Sundorf et al. [17]</td>
<td>94</td>
<td>PF</td>
<td>53 57.5</td>
<td>38 40</td>
<td>n.s.</td>
</tr>
<tr>
<td>Chiara et al. [18]</td>
<td>58</td>
<td>Cisplatin</td>
<td>78 72</td>
<td>81 83</td>
<td>n.s.</td>
</tr>
<tr>
<td>Souhami et al. [19]</td>
<td>107</td>
<td>BOMP</td>
<td>47 32.5</td>
<td>23 39</td>
<td>0.02</td>
</tr>
<tr>
<td>Tattersall et al. [20]</td>
<td>260</td>
<td>EpP</td>
<td>72 92</td>
<td>47 70</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Adapted from [2]. BIP = Bleomycin, ifosfamide and cisplatin; BOMP = bleomycin, vincristine, mitomycin C and cisplatin; BOP = bleomycin, vincristine and cisplatin; EpP = epirubicin and cisplatin; MtxCVP = methotrexate, chlorambucil, vincristine and cisplatin; PEPc = cisplatin, epirubicin and cyclophosphamide; PF = cisplatin and fluorouracil; n.s. = not significant.
95% CI = 0.53–0.80, p = 0.0004) indicated a highly significant reduction in the risk of death with NACT, but there were some differences between the trials in their design and results [22].

In a meta-analysis, Kim et al. [32] reviewed data of five randomized trials and four observational studies. In patients with stage IB1–IIA, NACT prior to surgery reduced the need for adjuvant radiation therapy by decreasing tumor size and lymph node metastasis, and distant metastasis but it failed to improve survival compared to patients who underwent primary surgery [32]. Rydzewska et al. [33], for the Cochrane Database of Systematic Reviews, have recently analyzed the results of six randomized studies. Both overall survival (HR = 0.77, 95% CI 0.62–0.96, p < 0.02) and progression -free survival (PFS) were significantly improved with NACT (HR = 0.75, 95% CI = 0.61–0.93, p = 0.008). There was no difference in the effect of NACT with respect to total cisplatin dose, chemotherapy cycle length or cervical cancer stage [33].

Thus, NACT administered at a shorter interval (e.g. weekly) prior to radical surgery for patients with early-stage cervical cancer (IB2, IIA) appears to be associated with an improved response rate and progression-free survival. However, the impact on overall survival remains to be confirmed.

**NACT for Fertility-Preserving Surgery**

NACT is now routinely used for eligible patients prior to breast-conserving surgery and for limb-sparing surgery in osteosarcoma. A number of case reports and small studies have suggested that NACT can be considered in young patients with early disease (FIGO IB1) desirous of fertility preservation. Kobayashi et al. [34] from Japan first reported a successful pregnancy and freedom from disease in a patient of stage IB1 cervical cancer following NACT therapy and conization. Maneo et al. [35] treated 51 patients of stage IB1 cervical cancer with three courses of cisplatin, paclitaxel and ifosfamide followed by cervical conization and pelvic lymph node sampling. Whenever the frozen section of the lymph node was positive, radi-
cal hysterectomy was performed. Five patients achieved pathological CR following NACT. After a median 69-month follow-up, no relapse was observed. A total of 10 pregnancies occurred resulting in 9 live births and 1 first-trimester abortion [35]. In a recent report, Wang et al. [36] reviewed data on 42 patients including 2 cases from their own experience. CR or optimum pathological response was seen in 81.5% of patients following NACT. Twenty-eight pregnancies, 1 first-trimester loss and 5 premature deliveries were reported. The high rate of pathological response confirms the effectiveness of preoperative chemotherapy for reducing the tumor volume and allowing the removal of a cervical cone only instead of the entire cervix [36].

Thus, NACT followed by fertility-preservation surgery appears to be a feasible approach for young women with bulky stage IB1. Following 2–3 cycles of NACT, more than 50% of patients achieve pathological CR and have a good reproductive outcome. A tumor size of >2 cm and a stromal invasion depth of >50% are risk factors for recurrence.

Concurrent Chemoradiation

In the year 1999 and later, several randomized studies demonstrated a therapeutic advantage of combining chemotherapy with radiation (CCRT) over RT alone (Table 5). In these studies, cisplatin was used either alone or with 5-fluorouracil. The positive results of these trials [37–42] and subsequent meta-analyses have led to a change in the management of cervical cancer [43–45]. A recent meta-analysis of thirteen trials confirmed an absolute benefit of 6% in overall survival at 5 years with CCRT (HR = 0.81, p < 0.001). A larger survival benefit was seen for the two trials in which chemotherapy was administered after CCRT with an absolute improvement of 19% at 5 years. Survival benefit was seen for both the group of trials that used platinum-based (HR = 0.83, p = 0.017) and non-platinum-based (HR = 0.77, p = 0.009) CCRT, but no difference was seen in the size of the benefit by RT or chemotherapy dose or scheduling. CCRT also reduced local and distant recurrence and progression and improved disease-free survival. The benefit was higher for patients with early-stage disease (7–10% for stage I–II vs. 3% for stage III). With CCRT, a 5-year overall survival rate of 66% and disease-free survival of 58% was achieved in these patients with locally advanced disease. Acute hematological and gastrointestinal toxicities were more frequent in the CCRT group [44]. The findings of this meta-analysis were further supported by a recent Cochrane review: CCRT improved overall survival and progression-free survival, whether or not platinum was used with absolute benefits of 10 and 13%, respectively. The effect was greater in trials including a high proportion of stage I and II patients [45].

In a recent meta-analysis of four randomized trials and four retrospective studies (n = 1,500) using single-agent cisplatin along with radiation versus cisplatin-based doublet chemotherapy along with radiation, there was improved overall survival (OR 0.65, 95% CI 0.51–0.81, p < 0.0002) and progression-free survival (OR 0.71, 95% CI 0.55–0.91, p = 0.006) and a reduced rate of locoregional relapse (OR 0.64, 95% CI 0.47–0.89, p = 0.008) for patients (FIGO stage IB–IVA) who received cisplatin-based doublet chemotherapy along with radiation [46].

### Table 5. CCRT versus RT: overall survival

<table>
<thead>
<tr>
<th>Authors [Ref.]</th>
<th>Drugs</th>
<th>Patients, n</th>
<th>Stage</th>
<th>CCRT, %</th>
<th>RT, %</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morris et al. [37]</td>
<td>CF</td>
<td>386</td>
<td>IB or IIA (≥5 cm or PLN+) IIB, III, IVA</td>
<td>73</td>
<td>38</td>
<td>0.004</td>
</tr>
<tr>
<td>Keys et al. [38]</td>
<td>C</td>
<td>389</td>
<td>Stage IB (≥4 cm)</td>
<td>84</td>
<td>68</td>
<td>0.008</td>
</tr>
<tr>
<td>Peters et al. [39]</td>
<td>CF</td>
<td>241</td>
<td>IA2, IB, IIA (with high postoperative risk)</td>
<td>81</td>
<td>63</td>
<td>0.01</td>
</tr>
<tr>
<td>Whitney et al. [40]</td>
<td>CF/H</td>
<td>388</td>
<td>IIB, III, IVA</td>
<td>50.8</td>
<td>39.8</td>
<td>0.01</td>
</tr>
<tr>
<td>Rose et al. [41]</td>
<td>C vs. H</td>
<td>526</td>
<td>IIB, III, IVA</td>
<td>64</td>
<td>39</td>
<td>0.002</td>
</tr>
<tr>
<td>Rose et al. [47]</td>
<td>CHF vs. H</td>
<td>526</td>
<td>IIB, III, IVA</td>
<td>60</td>
<td>39</td>
<td>0.002</td>
</tr>
<tr>
<td>Pearcey et al. [42]</td>
<td>C</td>
<td>253</td>
<td>IB2, IIA (≥5 cm), IIB, III, IVA</td>
<td>3-year OS = 69</td>
<td>66</td>
<td>0.42</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5-year OS = 62</td>
<td>58</td>
<td>0.33</td>
</tr>
</tbody>
</table>

Modified from [2]. C = Cisplatin; H = hydroxyurea; F = 5-fluorouracil; OS = overall survival; PFS = progression-free survival.
Thus, two analyses endorse the recommendations made in the NCI alert, but with far greater reliability and precision regarding the gains of CCRT [45]. A review of the various phase III randomized trials, long-term follow-up [47] and meta-analyses indicates that, although chemoradiation is a standard form of treatment for early cancer of the cervix, its role in advanced stages needs further exploration [48].

**Dose-Dense NACT prior to CCRT**

A dose-dense weekly schedule has been shown to be well tolerated and associated with improved outcome in head and neck [49], breast [50] and ovarian cancer [51]. These observations suggest a possible role for a weekly schedule; a dose-dense schedule is likely to result in an improvement in outcome. Paclitaxel and carboplatin combination has been used in a weekly schedule in a number of cancers both as adjuvant treatment (breast, ovary, head and neck, lung) and treatment of recurrent disease (breast, ovary, and lung). This combination maximizes potential additive/synergistic interactions with different mechanism of actions. A weekly schedule is both dose dense and dose intense [49–51]. Initial results from two phase II studies have been reported recently. Patients received NACT using weekly paclitaxel (60–80 mg/m²) and carboplatin (AUC – 2) for 6 weeks followed by concurrent CCRT. Following NACT, a response rate of 67.5–70% was achieved, mostly being partial responses. After CCRT, 85–100% of eligible patients achieved CR. Grade 3–4 hematologic toxicity was seen in about 20% of patients. These observations are encouraging [52, 53] and need confirmation in a randomized study.

**Adjuvant Chemotherapy**

Few randomized studies have studied if adjuvant chemotherapy after primary treatment – surgery or RT – can improve outcome. Recently, Rosa et al. [54], for the Cochrane database, have analyzed three studies and concluded that adjuvant platinum-based chemotherapy after chemoradiation may improve survival in women with early-stage cervical cancer (stage IA2–IIA) with presence of risk factors for recurrence [54]. Prognostic factors which indicate higher risk of recurrence after surgery are (i) lymph node metastasis, (ii) lymphovascular space invasion, (iii) invasion depth of more than 10 mm, (iv) microscopic parametrial invasion, (v) non-squamous histology and (vi) positive surgical margins [54].

For locally advanced cervical cancer (IIB–IVA), two randomized studies have evaluated the role of adjuvant chemotherapy (Cochrane database review); however, there was significant heterogeneity regarding the use of CCRT chemotherapy in the first study and the choice of chemotherapy as adjuvant (non-platinum) in the second trial. Quality of life (QOL) was not studied in either of these studies [54].

Thus, at present, data on the use of adjuvant chemotherapy in locally advanced cervical cancer is insufficient and there is a need for randomized trials to demonstrate the efficacy, toxicity and effect on quality of life [54].

**Targeted Treatment**

Preclinical studies in cervix cancer have identified several molecular pathways that are involved in cellular proliferation, interaction with angiogenesis, extracellular matrix adhesion/invasion, apoptosis, cell cycle pathways and DNA repair mechanisms (table 6). Vascular endothelial growth factor receptor (VEGFR) and epidermal growth factor receptor (EGFR) are upregulated in the majority of cervical cancers [55–57]. EGFR overexpression has been shown to correlate...
relate with resistance to cytotoxic chemotherapy and radiation in squamous cervical cancer [57]. 54–71% of squamous cervical cancers express EGFR. Two monoclonal antibodies, e.g. cetuximab (a chimeric immunoglobulin G2 monoclonal antibody targeting the extracellular domain of the EGFR) and matuzumab (humanized immunoglobulin G1 monoclonal antibody), have been used either as a single agent or in combination with cisplatin or cisplatin and topotecan. Unfortunately, response rates have been poor with minimal benefit on progression-free and overall survival when used for the treatment of both recurrent and persistent cervical carcinoma [reviewed in 57]. Tyrosine kinase inhibitors result in the inhibition of phosphorylation and signal transduction interruption. Two small molecules, e.g. gefitinib and erlotinib, have been used in patients with recurrent and persistent cervix cancer with a lack of objective responses. A study with lapatinib (leading to Her-2-neu inhibition) showed a 5% objective response rate [57].

A phase II randomized trial studied pazopanib and lapatinib: the pazopanib arm showed a trend to prolonged progression-free survival (HR = 0.66, 90% CI 0.48–0.91) with a favorable toxicity profile (grade 3 and grade 4 adverse events around 10–12%). However, this study seems to be underpowered [58].

Bevacizumab is a monoclonal antibody directed against VEGF-A and has been used with the aim to normalize the abnormal tumor vasculature, increase tumor oxygenation, and reduce interstitial fluid pressure [56]. Recently, Tewari et al. [59], for the Gynecologic Oncology Group (GOG study 240), have evaluated the effectiveness of bevacizumab (15 mg/kg) in 452 patients with recurrent, persistent, or metastatic cervical cancer. Patients were randomly assigned to 1 of 4 treatment groups, 2 of which received bevacizumab. Chemotherapy consisted of cisplatin at a dose of 50 mg/m² plus paclitaxel at a dose of 135 or 175 mg/m² or topotecan at a dose of 0.75 mg/m² on days 1–3 plus paclitaxel at a dose of 175 mg/m² on day 1. Cycles were repeated every 21 days until disease progression. Topotecan-paclitaxel was not superior to cisplatin-paclitaxel (HR for death = 1.20). With the data for the two chemotherapy regimens combined, the addition of bevacizumab to chemotherapy was associated with increased overall survival (17.0 vs. 13.3 months; HR for death = 0.71, 90% CI 0.54–0.95, p = 0.004) and higher response rates (48 vs. 36%, p = 0.008). Bevacizumab, as compared with chemotherapy alone, was associated with an increased incidence of hypertension of grade 2 or higher (25 vs. 2%), thromboembolic events of grade 3 or higher (8 vs. 1%), and gastrointestinal fistulas of grade 3 or higher (3 vs. 0%) [59].

Thus, though a number of molecular pathways have been identified as potential therapeutic targets in the treatment of cervical cancer. So far, phase III data is available for bevacizumab blocking angiogenesis [59]. Whether to use bevacizumab as a single agent or in combination with chemotherapy with or without maintenance, the dose (15 mg/kg vs. lower dose) and cost are currently open-ended questions and are likely to be answered in future studies [59, 60].

Summary

The current management of cervical cancer requires a multidisciplinary team approach. For patients with early disease, the decision to go for upfront surgery or radiation or the use of NACT prior to surgery or fertility preservation surgery should be based on a careful review of clinical findings, imaging, pathology and availability of surgical skills, which allows the patients to make an informed decision towards initial therapy. The use of dose-dense chemotherapy prior to CCRT and adjuvant chemotherapy after chemoradiation in high-risk patients are other potential areas for future research.

Disclosure Statement

The authors declare no conflict of interest.

References


