Radio-chemotherapy in Cervical Cancer: Proved Efficacy

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For patients with locally advanced cervical cancer the standard choice of treatment until 1999 was radical radiotherapy with modest results. In that year, the results of five randomized trials led to a National Cancer Institute recommendation that concomitant chemoradiotherapy should be considered standard care for women with cervical cancer. Two Cochrane reviews by Green from 2001 and 2005 concurred with this recommendation. In the new Cochrane review published by Vale in 2010 there was a 6% improvement in 5-year survival with chemoradiotherapy (HR =0.81, P < 0.001). At the “Prof.Dr.Ion Chiricuță” Oncology Institute Cluj-Napoca, two randomized phase III single institutional studies were completed. The first study was initiated in 1999, and compared radiotherapy (RT) to concurrent radio-chemotherapy (RTCT) in locally advanced (IIB-IIIB) cervical carcinoma. 566 patients were included in the RT arm (284 patients) and in the RTCT arm with cisplatin 20 mg/m²×5 days, at 21 days (282 patients). The results showed the benefits of concurrent RTCT compared to RT alone in patients with locally advanced cervical carcinoma, regarding local control (78% vs. 67%) and 5 year survival rates (74% vs. 64%) (p < 0.05). In 2003 at the “Prof.Dr.Ion Chiricuță” Oncology Institute “the second randomized phase III study was initiated which compared two concomitant RTCT regimens in stage IIB-IIIB cervical carcinoma. 326 patients were randomly assigned in the two arms of the protocol: 164 in the RTCT arm with cisplatin 20 mg/m²×5 days at 21 days and 162 in the RTCT arm with weekly 40 mg/m² cisplatin. The local control was significantly superior (87% vs 75%, p<0.01) and the 5 year overall survival was 6% better (78% vs 72%, p=0.14) in the 5 day regimens’ arm in comparison with the weekly cisplatin arm. Several molecular targeted agents possessing radiosensitizing properties opened the way for their testing either alone or with known cytotoxic radiosensitizers for cervical cancer. These results proved the obvious superiority of chemoradiotherapy compared with radiotherapy for women with cervical cancer.

Key words: Cervical cancer, Radiochemotherapy, Radiosensitizer.

Epidemiology

Cervical cancer remains one of the greatest killers of women worldwide. According to Globocan 2008, it is estimated that in 2008 the number of patients diagnosed with and those who died from this disease was 529,828 and 275,128, respectively (1). It is remarkable that these rates occur, despite the fact that cervical cancer is a model for early detection due to its long and relatively well-known natural history that offers an excellent opportunity for its detection before lesions become invasive (1).

Romania ranks first in Europe regarding the incidence and mortality caused by cervical carcinoma. In the last 30 years a slow but continuous increase in incidence was observed: in 1980 the incidence was 19.04%000 and increased to 23.9%000 in 2008, with 3402 new cases and 2005 deceased (1).

Among new diagnosed and treated tumours at the “Prof.Dr.Ion Chiricuță” Oncology Institute Cluj-Napoca, cervical cancer is on the second place; the number of cases has doubled in the last 10 years, from 565 in 1998 to 1158 in 2008 (2). 70% of these new diagnosed cases are in advanced stages, in which the results of classical treatment are modest.

Treatment of locally advanced stages

Treatment of locally advanced cervical cancer experienced no major changes for nearly 30 years during which exclusive radiation was considered the standard of care (3); thus, 5-year survival for stages IB2, IIB, IIIB, and IVA are 72.2, 63.7, 41.7, and 16.4%, respectively, according to the 1998 Annual Report on the Results of Treatment in Gynecological Cancer (4). The lengthy permanence of this unimodal treatment was due, on the one hand, to the classical concept that cervical cancer is a disease that progresses in an orderly fashion (local, then regional, and at the very last, systemic); therefore, it could be effectively treated with a local modality such as radiation instead of a systemic
modality such as chemotherapy. On the other hand, the role of surgery for locally advanced cases failed to treat the disease successfully by radical surgical procedures. Although increasing the dose of radiation improves the control of pelvic disease, the dose that can be delivered is limited by the severe late complications of the treatment. There have been no substantial improvements in the treatment of cervical cancer since the advent of megavoltage irradiation in the 1950s. Many attempts have been made to improve the outcome of radiotherapy, but none of these have been successful. As a result, strategies involving combination therapy, especially the concurrent use of chemotherapy with radiotherapy, have been considered.

The administration of chemotherapy concurrently with radiotherapy has theoretical advantages over the use of radiotherapy alone. The two treatments may interact to increase the killing of tumor cells without delaying the course of radiotherapy or protracting the overall treatment time, which may accelerate the proliferation of tumor cells. Theoretically, chemotherapy may act synergistically with radiotherapy by inhibiting the repair of radiation-induced damage, promoting the synchronization of cells into a radiosensitive phase of the cell cycle, initiating proliferation in nonproliferating cells, and reducing the fraction of hypoxic cells that are resistant to radiation. Chemotherapy may also independently increase the rate of death of tumor cells. Nevertheless, since the doses of chemotherapeutic drugs that are administered concurrently with radiation are less than the usual amounts used for solid tumors, it is not likely that such treatment will affect any distant metastases that may be present.

**Platinum-based chemoradiation**

Over the last 20 years, a number of trials testing concurrent chemoradiation were performed in an attempt to improve treatment results. Despite this, in 1996 a National Institute of Health Consensus Statement on cervical cancer stated that there was no evidence that hydroxyurea or any other concomitant chemotherapeutic agent should be added to pelvic irradiation and incorporated into standard practice (6). It was not until 1999 that five randomized studies including nearly 2,000 patients were published, demonstrating that survival rate with concomitant chemotherapy (RT/CT) based on cisplatin was superior than that obtained with radiation alone (5, 6, 7, 8, 9).

The well-conducted study by Keys et al. (5) for the Gynecologic Oncology Group, compared radiotherapy alone with a regimen of six weeks of cisplatin and pelvic irradiation, given concurrently in 369 patients with node-negative bulky stage IB cervical cancer. The combined regimen was well tolerated and did not increase the median treatment time, which was 50 days in both groups. The concurrent use of cisplatin and radiation in this particular stage of cervical cancer significantly improved control of pelvic disease and prolonged survival.

Rose et al. (6) assessed data on 526 women with stage IIB, III, or IVA cervical cancer who were randomly assigned to receive radiotherapy concomitantly with one of three chemotherapy regimens: weekly cisplatin; two courses of a three-drug combination consisting of hydroxyurea, cisplatin, and fluorouracil; or twice-weekly hydroxyurea. Almost half the patients in this study had disease involving the pelvic wall (stage IIIB) or the bladder (stage IVA). The progression-free survival rates at 24 months were significantly higher in the two groups that received cisplatin (67% and 64%) than in the group that received hydroxyurea (47%). Because there was less toxicity with cisplatin alone, than with the three-drug regimen, the former is probably the preferable regimen to use in combination with radiotherapy. The results of this study send a clear message that it is time to abandon the use of hydroxyurea, which has never been widely accepted as a treatment for cervical cancer.

The study by Morris et al. (7) involved 388 women with a spectrum of advanced disease ranging from bulky stage IB through stage IVA. The women were assigned to receive either three cycles of cisplatin and fluorouracil in combination with pelvic radiation or irradiation of the pelvis and para-aortic lymph nodes alone. Morris et al. used a higher dose of radiation and a somewhat shorter overall treatment time than Rose et al. (median, 58 days vs. 63 days). The addition of chemotherapy improved the control of pelvic disease and significantly increased overall survival rates (73%, as compared with 58% with the use of irradiation alone).

The results of the five trials listed in Table I show similar reductions in the risk of death from cervical cancer and similar absolute improvements in survival.

The promising results of the five studies prompted the National Cancer Institute to issue a rare clinical announcement that “strong consideration should be given to the incorporation of concurrent cisplatin-based chemotherapy with radiation therapy in women who require radiation therapy for treatment of cervical cancer”, except for patients with comorbidities who are radiated for stage IB1 or less” (10).
The results of a prospective randomized trial elaborated and conducted in the Oncology Institute Cluj overlap with the results published in these trials.

In our randomized unicentric phase III study, 566 patients with squamous cell cervical carcinoma were included between 1999-2002: 284 in arm A (RT) and 282 in arm B (concurrent RTCT with cisplatin 20 mg/m² x 5 days). 238 (42%) were in stage IIB, 209 (37%) in IIIA, and 119 (21%) in IIIB. The local control (78% vs 67%) and the 5 year survival rate was statistically significant superior in the concurrent RTCT group (74%) versus RT group (64%) (p<0.05) (Fig. 1). In patients operated after RT or RTCT superior results were obtained, compared to the non operated patients: 86% versus 53% five year survival rate (p<0.01) (Fig. 2). 192 failures were registered: 109 (38%) in cases of RT alone versus 83 (29%) after concurrent RTCT (p<0.01). The results of our randomized study prove the obvious superiority of concurrent RTCT with 5-day cisplatin compared with RT alone in patients with locally advanced cervical carcinoma (11).

Although it is widely accepted that cisplatin-based chemoradiation is the standard treatment for locally advanced cervical carcinoma, optimal scheduling and dosing have yet to be established. Evidence from the GOG125 study indicates that weekly cisplatin at 40 mg/m² for six weeks is equally effective yet less toxic than cisplatin and 5-fluorouracil in a classic 21-day schedule (6); nonetheless, the choice of 40 mg/m² as the dose for weekly cisplatin for phase III chemoradiation trials was not based on previous phase I data, and the maximum tolerated dose of weekly cisplatin in combination with pelvic radiation has not been clearly defined.

In 2003 the second randomized phase III study from our Institute compared two concomitant RTCT regimens in stage IIB-IIIB cervical carcinoma. 164 patients were assigned in RTCT arm with cisplatin 20 mg/m² x 5 days at 21 days and 162 in RTCT arm with weekly 40 mg/m² cisplatin. The 5 year overall survival (78% vs 72%, p=0.14) and disease free survival (73% vs 69%, p=0.09) was superior in the 5 day regimens’ arm in comparison with the weekly cisplatin arm, despite the fact that the difference was not statistically significant. However, local-free survival at 5 years was significantly superior in the arm with cisplatin during 5 consecutive days. (87%, CI 80%-91%) vs weekly cisplatin (77%, IC 69%-73%), p<0.01 (Fig. 3) (12).

In terms of quality of life (EORTC QLQ-30, v.3.0 questionnaire) and acute toxicity (CTC v.2.0) concomitant RTCT with cisplatin 20 mg/m² x 5 days has a better impact on patients’ QoL and lower toxicity compared with weekly chemotherapy regimen (12).

Carboplatin and cisplatin have an identical mechanism of cytotoxicity; the therapeutic carboplatin dose relative to the therapeutic cisplatin dose has been described as a ratio of 4:1 (400–500 mg/m² vs. 100 mg/m²), based on clinical studies in ovarian cancer (13). Despite the fact that weekly cisplatin during radiation is well-tolerated, its nephrotoxicity is of particular concern in a patient population that frequently harbor renal dysfunction as a consequence of ureteral obstruction by the disease spreading to the pelvic wall or to the bladder. Although <10% of patients with bulky tumors with uni or bilateral ureteral obstruction present abnormal creatinine serum levels (14), subclinical changes in renal function are known to occur in renal obstructive disease (15).

There are some reports on use of carboplatin concurrently to radiation. In a report on carboplatin as radiosensitizer, 22 patients staged from IIA-IIIB were treated with 30 mg/m² twice a week with escalation at 40 mg/m² and 50 mg/m²; however, after several patients were treated, the dose was re-calculated according to the area under the curve (AUC).

Accordingly, the authors suggest that an AUC of 6 could be adequate on the basis that only two of nine patients presented leukopenia grade 3 (16). In a phase I study of weekly carboplatin during radiation, 24 FIGO stage IIIB patients were treated with standard pelvic radiation concurrently with six weekly applications of carboplatin at the following dose levels: I (100 mg/m²); II (116 mg/m²); III (133 mg/m³), and IV (150 mg/m²). The treatment was well tolerated; the median number of weekly applications of carboplatin was six, and the dose-limiting toxicity (leucopenia and/or neutropenia) was present in 50% of patients treated at the higher-dose level (150 mg/m³). This occurred in 33% of patients at 133 mg/m² and hence, this dose was that recommended for use in further trials. Remarkably, the clinical response rate was similar to that reported for standard cisplatin (17).
Table I: Estimates of the relative risk of death in five clinical trials of concurrent chemotherapy and radiotherapy.

<table>
<thead>
<tr>
<th>STUDY</th>
<th>FIGO STAGE</th>
<th>CONTROL GROUP</th>
<th>COMPARISON GROUP</th>
<th>RELATIVE RISK OF DEATH IN COMPARISON GROUP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keys et al.[5]</td>
<td>IB2</td>
<td>Radiotherapy</td>
<td>Radiotherapy plus weekly cisplatin</td>
<td>0.54</td>
</tr>
<tr>
<td>Rose et al.[6]</td>
<td>IIB–IVA</td>
<td>Radiotherapy plus hydroxyurea</td>
<td>Radiotherapy plus weekly cisplatin Radiotherapy plus cisplatin, fluorouracil, and hydroxyurea Radiotherapy plus cisplatin Radiotherapy plus cisplatin, fluorouracil, and hydroxyurea</td>
<td>0.61 0.58</td>
</tr>
<tr>
<td>Morris et al.[7]</td>
<td>IB2–IVA</td>
<td>Extended-field radiotherapy</td>
<td>Radiotherapy plus cisplatin and fluorouracil</td>
<td>0.52</td>
</tr>
<tr>
<td>Whitney et al.[9]</td>
<td>IIB–IVA</td>
<td>Radiotherapy plus hydroxyurea</td>
<td>Radiotherapy plus cisplatin and fluorouracil</td>
<td>0.72</td>
</tr>
<tr>
<td>Peters et al. [8]</td>
<td>IB or IIA (selected postoperatively)</td>
<td>Radiotherapy</td>
<td>Radiotherapy plus cisplatin and fluorouracil</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Fig. 1. Five year survival by treatment group: radiotherapy (RT) versus radiochemotherapy (RTCT).

Fig. 2: Five year survival at operated (RT+CT+S) versus non operated (RT+CT) patients.
New radiosensitizers

Topotecan
Clinical studies with these agents as radiosensitizers are limited in cervical cancer. In some phase I trials topotecan was concomitantly administered with standard radiotherapy in advanced squamous cell carcinoma of the cervix, setting the dose which determines the accepted toxicity (18). Currently, a phase I study (GOG-9913 and NCT00054444) of the combination of topotecan and cisplatin plus standard radiation is ongoing.

Paclitaxel
Paclitaxel either alone or in combination with other agents has undergone evaluation as a sensitizer in cervical cancer. A pilot study of concurrent radiotherapy and weekly paclitaxel for locally advanced or recurrent squamous cell carcinoma of the uterine cervix was reported by an Italian study. The authors administered paclitaxel weekly at 40 or 60 mg/m$^2$ during the entire external radiotherapy course. A total complete response rate of 63% was obtained (19).

Three dose-finding studies have been performed combining either carboplatin or cisplatin with paclitaxel. The first study was intended to determine the tolerable doses and potential toxicities of taxol, administered weekly, with concomitant cisplatin and radiation therapy in advanced cervical cancer. The authors suggest that 50 mg/m$^2$ of paclitaxel every week during external radiation concurrent with cisplatin at 50 mg/m$^2$ every 21 days is safe and effective in these patients (20). Later, a second phase I study was reported in which the maximal tolerated dose was paclitaxel at 50 mg/m$^2$ in this regimen of weekly cisplatin at 30 mg/m$^2$. Overall response rate was 92.3%, suggesting that this scheme is effective for cervical cancer treatment (21). A third study was conducted to determine the maximum tolerated dose (MTD) and dose-limiting toxicity (DLT) of weekly paclitaxel/carboplatin chemoradiotherapy in locally advanced cervix cancer. The maximum tolerated dose of carboplatin was 2.5 AUC with 50 mg/m$^2$ of paclitaxel. Responses were encouraging, with estimated progression-free and overall survival of 80 and 86%, respectively (22).

Gemcitabine
The results of a phase II trial in which they chose the dose of 300 mg/m$^2$ weekly for 5 weeks during external radiation, for FIGO stage IIIB patients, the disease-free and overall survival were 84 and 100%, respectively (23).

The high activity and tolerability of gemcitabine during radiation was also reported in patients suffering from ureteral tumor obstruction-associated renal dysfunction. In this report, eight cervical carcinoma patients whose serum creatinine ranged from 1.6–18.5 mg/100 mL (median, 3.3; mean, 6.8) received gemcitabine at 300 mg/m$^2$ concurrent with standard pelvic radiation. The authors suggest that ureteral obstruction causing any degree of renal insufficiency should not be a contraindication for receiving chemoradiation to attempt a cure and that in this setting in which cisplatin is
A surrogate marker of survival (26) between the experimental arm of cisplatin 40 mg/m² and gemcitabine and particularly in combination with cisplatin, a phase II randomized study was initiated primarily to compare rate of pathologic complete response as radiosensitizers over cisplatin alone. In this study, there was no evidence on the superiority of any combination regimen. Acute hematological and gastrointestinal toxicity was significantly higher in the concomitant chemotherapy group. Treatment-related deaths were rare, but late effects of treatment were not well-reported; thus, the impact of chemoradiation on these effects could not be determined adequately (27).

Despite these encouraging results with gemcitabine and particularly in combination with cisplatin, there was no evidence on the superiority of any combination of radiosensitizers over cisplatin alone. In this line, a phase II randomized study was initiated primarily to compare rate of pathologic complete response as a surrogate marker of survival (26) between the experimental arm of cisplatin 40 mg/m² and gemcitabine 125 mg/m² vs. cisplatin alone (40 mg/m²). In this study, patients staged as IB2, IIA, and IIB. Complete pathologic response in the cisplatin group was 55%, (95% CI, 35.5–73) and 77.5% (95% CI, 57–90) for the gemcitabine cisplatin arm (p = 0.0201). The combination regimen was more toxic and had fewer weekly doses delivered and a lower cisplatin dose-intensity, which resulted in a longer time to complete external radiation in the experimental arm. (27)

These results strongly supported the high efficacy of this combination and led to the design of a multicenter, open label, randomized phase III study comparing concurrent gemcitabine (Gem) plus cisplatin (Cis) and radiation followed by adjuvant Gem plus Cis versus concurrent Cis and radiation in patients with stage IIB to IVA carcinoma of the cervix. Overall survival at 3 years was statistically superior to Gem/cis/rad (78.2%) over Cis/rad (69.1%) (p=0.022, HR=0.68, 95%CI=0.49-0.95). Local control was numerically improved in Gem/cis/rad arm, with 11.2% local failure vs 16.4% in Cis/rad arm (p=0.097), the distant failures also was significantly reduced (8.1%) by Gem/cis/rad in comparison with Cis/rad(16.4%) arm (p=0.009). This novel regimen significantly improved outcomes in patients with locally advanced carcinoma of the cervix, at the expense of increased but acceptable toxicity, compared to the current standard of care. (28)

Meta-analysis provides strong support for chemoradiotherapy in cervical cancer

A meta-analysis based on 19 trials (17 published and two unpublished) including 4,580 patients corroborated these findings, confirming that chemoradiation improves overall survival (HR 0.71, p<0.0001), whether platinum was used (0.70, p<0.0001) or not (0.81, p=0.20). An improvement in progression-free survival was also seen with chemoradiation (0.61, p<0.0001). Thus, the absolute benefit in progression-free and overall survival was 16% (95% CI 13-19) and 12% (8-16), respectively. A significant benefit of chemoradiation on both local (odds ratio 0.61, p<0.0001) and distant recurrence (0.57, p<0.0001) was also recorded (Fig. 4) (29).

An update of the aforementioned meta-analysis that includes 24 trials (21 published, three unpublished) and 4,921 patients strongly suggests that chemoradiation improves overall survival and progression-free survival, whether or not platinum was used, with absolute benefits of 10 and 13%, respectively. There was, however, statistical heterogeneity for these outcomes. There was some evidence that the effect was greater in trials including a high proportion of stage I and II patients. Chemoradiation also showed significant benefit for local recurrence and the suggestion of a benefit for distant recurrence. Acute hematological and gastrointestinal toxicity was significantly higher in the concomitant chemoradiation group. Treatment-related deaths were rare, but late effects of treatment were not well-reported; thus, the impact of chemoradiation on these effects could not be determined adequately (30).

A meta-analysis published in 2010 by C.L. Vale on the basis of 13 trials that compared chemoradiotherapy versus the same radiotherapy, demonstrated a 6% improvement in 5-year survival with chemoradiotherapy (hazard ratio (HR) = 0.81, P < 0.001). A larger survival benefit was seen for the two trials in which chemotherapy was administered after chemoradiotherapy. There was a significant survival benefit 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) chemoradiotherapy, but no evidence of a difference in the size of the benefit by radiotherapy or chemotherapy dose or scheduling was seen. Chemoradiotherapy also reduced local and distant recurrence and progression and improved disease-free survival (DFS) (31).

These results endorse the recommendations of the NCI alert, but also demonstrate their applicability to all women and a benefit of nonplatinum
based chemoradiotherapy. Furthermore, although these results suggest an additional benefit from adjuvant chemotherapy this requires testing in further trials.

<table>
<thead>
<tr>
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<th>O-E</th>
<th>Variance</th>
</tr>
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<tbody>
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<td>108/191</td>
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<td>45.45</td>
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<tr>
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<td>22/62</td>
<td>3.69</td>
<td>11.25</td>
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<tr>
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<td>71/193</td>
<td>-19.13</td>
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<tr>
<td>Peters</td>
<td>21/127</td>
<td>36/116</td>
<td>-9.60</td>
<td>14.25</td>
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<tr>
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<td>49/186</td>
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<td>17.86</td>
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<td>89/177</td>
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<td>52/126</td>
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<td>39/78</td>
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<td>466/1129</td>
<td>-72.72</td>
<td>204.27</td>
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<table>
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<td>6/18</td>
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<td>34/110</td>
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<td>Roberts</td>
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<td>Subtotal</td>
<td>62/228</td>
<td>70/206</td>
<td>-6.30</td>
<td>29.16</td>
</tr>
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</table>

| Total       | 467/1521  | 536/1335| -79.02 | 233.43   |

Fig. 4: Results for overall survival (29).
Molecular-targeted therapies as radiosensitizers

The current preclinical and clinical availability of a number of newer products collectively termed “molecular targeted agents” has led to their study as new forms of radiosensitization. A few ongoing clinical trials have evaluated these drugs as radiosensitizers in cervical cancer:

- Cetuximab, cisplatin, and radiation therapy in treating patients with stage IB, stage II, stage III, or stage IVA cervical cancer (GOG-9918, NCT00104910)
- A phase I-II study of the COX-2 inhibitor celecoxib and chemoradiation in patients with locally advanced cervical cancer (RTOG C-0128)
- Radiation therapy plus celecoxib, fluorouracil, and cisplatin in patients with locally advanced cervical cancer (NCT00023660)
- Phase II trial of the combination of DNA methylation inhibitor hydralazine and the histone deacetylase inhibitor magnesium valproate added to cisplatin chemoradiation in FIGO stage IIIB patients (32).

Conclusion

The results of these studies, which prove the superiority of radiochemotherapy compared to radiotherapy, endorse the recommendations of the NCI alert and suggest as ”gold standards” concomitant radiochemotherapy in the treatment of locally advanced cervical cancer or early stages with unfavorable prognostic factors. This represents an important step forward in the treatment of patients with cervical cancer.

The chemoradiation trials proved the efficacy and good toxicity profile of cisplatin, and positioned it as the standard agent to be used to sensitize cancer cells to radiation in cervical cancer treatment. Newer cytotoxic agents with radiosensitizing properties, such as topotecan, paclitaxel, capecitabine, and gemcitabine, have demonstrated promising activity either alone or in combination with cisplatin in phase I studies or small phase II studies. In this line, gemcitabine is the newer cytotoxic agent with the most extensive evaluation. A randomized phase III trial demonstrated the superiority of the combination of standard cisplatin plus gemcitabine over cisplatin alone. Several molecular targeted agents possessing radiosensitizing properties have opened the way for their testing either alone or with known cytotoxic radiosensitizers for cervical cancer.

The meta-analysis demonstrated a significant survival benefit for both the group of trials that used platinum-based and non-platinum based chemoradiotherapy, but no evidence of a difference in the size of the benefit by radiotherapy or chemotherapy dose or scheduling was evidenced. Chemoradiotherapy also reduced local and distant recurrence and progression and improved disease-free survival. These results endorse the superiority of concurrent radio-chemotherapy in locally advanced cervical carcinoma and also demonstrate their applicability to all women with risk factors.

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