Novel agents and treatment techniques to enhance radiotherapeutic outcomes in carcinoma of the uterine cervix

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Background: Survival of patients with locally advanced carcinoma cervix (LACC) using the current standard of concurrent chemo-radiotherapy (CCRT) has reached a plateau over the last two decades. Loco-regional failure in first two years of treatment completion and distant metastasis in the subsequent years has put the survival curves at a halt. Strategies of induction and adjuvant chemotherapy have yielded little as has any advancement in techniques of delivery of radiation therapy. This article aims at discussing the current existing literature as well as promising novel strategies to enhance radiotherapeutic outcomes in carcinoma of the uterine cervix.

Methods: The review of English literature included phase I-III trials evaluating either a novel agent, novel application/modifications of an existing treatment regimen or an innovative treatment technique. The studies have been divided in to subsections with summary of most important findings at the end of each section.

Results: Despite CCRT being the 'gold standard' treatment, several issues like optimum drug combination, schedule of drug delivery, combination with molecular targeted agents etc. remain undefined. Taxane, topoisomerase and gemcitabine based regimen needs to be further explored and compared with cisplatin based CCRT regimen. Several approaches like local delivery of cytotoxic agents, use of nano-medicine with CCRT are appearing on horizon with promises for the future. Therapies need to be designed based on the human papillomavirus titers of the patients and incorporation of radiosensitizers as an effective way of palliation with short course of radiotherapy may further enhance the radiotherapeutic outcomes.

Conclusions: The results of the studies with novel agents and treatment techniques appear promising. Further research in this arena including incorporation of cost-effectiveness analysis and quality of life issues in future trial designs are warranted.

Keywords: Cervix uteri; radiation sensitizers; chemoradiotherapy; nanomedicine

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Introduction

Concurrent chemo-radiotherapy (CCRT) with cisplatin followed by brachytherapy has become the standard treatment for locally advanced (stage IB-IVA) cervical carcinoma (LACC) worldwide. The 5-year survival with this approach for LACC has reached a plateau (1) of 50–60% and this also comes at the cost of high toxicities (2). Modern techniques of radiation treatment has decreased the morbidities but has helped little in bringing any change in survival (3). Protocols other than CCRT like induction chemotherapy (4) or consolidative chemotherapy (5) have shown inconclusive advantage over CCRT alone and needs further exploration in well-designed trials. Thus, incorporation of novel agents, modification of existing protocols, intensification of regimens, and integration of local therapies with CCRT programs may be the way forward to improve and optimize the outcome of LACC patients. The present article discusses on the present evidence and future direction towards amalgamation of translational and clinical research in this arena and aims to ignite perspectives for the design of further clinical trials.

Modulation of existing CTRT protocols

Platinum based regimens

CCRT with weekly cisplatin remains the most widely used regimen worldwide and is the present gold standard to which other regimens should be compared (6). Three weekly regimens compared to weekly regimens suggested higher toxicity and delay of the treatment course with the former regimen (7). Most of the trials which formed the basis of current CCRT regimen used a combination of cisplatin and fluorouracil with or without hydroxyurea (1). Results of a randomized trial by Kim *et al.* (8) showed non-inferiority of weekly cisplatin to cisplatin plus fluorouracil combination; 4-year overall survival was 67% with cisplatin alone *vs.* 70% with combination and higher toxicity with the combination regimens (grade 3/4 hematological toxicity 43% *vs.* 26%; P=0.037).

Carboplatin is thought to be an active radio-sensitizer (9) and the side effect profiles may tempt clinicians to substitute it with cisplatin in certain situations like elderly patients, patient with renal dysfunction or with multiple co-morbidities (10). Katanyoo *et al.* (11) reported results of 148 patients of LACC treated with weekly concurrent carboplatin (AUC 2 or 100 mg/m^2) and found 5-year overall survival rates of 63.5% without any grade 3/4 toxicities. Au-Yeung *et al.* (12) in their retrospective audit of 442 patients of LACC showed inferior outcomes with weekly carboplatin as compared to cisplatin in terms of both disease free and overall survival. However, in the absence of a head to head comparative trial evaluating these regimens, the controversy remains unsettled.

Nedaplatin (an analogue of cisplatin) has been tried in a phase II study by Yokoyama *et al.* (13); 45 patients treated with concurrent nedaplatin showed a better toxicity profile as compared to cisplatin based regimens (grade 3 gastrointestinal toxicity of 4.4%; grade 4 hematological toxicity of 6.7%). Niibe *et al.* (14) reported 80% complete response rates for LACC with this approach in their study on 10 patients. A phase II study by Zhang *et al.* (15) also found combination of nedaplatin and paclitaxel to be tolerable (grade 3 or higher hematological toxicity of 10.9%) and effective with 2-year overall survival rate of 93% in 34 patients of LACC.

Taxane based regimens

The survival advantage with concurrent regimens has generated great enthusiasm in the search for newer regimens, drugs and schedules. Rao *et al.* (16) in a phase I clinical trial demonstrated feasibility and activeness of weekly paclitaxel/carboplatin with concomitant radiation. The maximum tolerated dose for paclitaxel was 50 mg/m^2 and for carboplatin was AUC 2.5. Two-year overall survival and progression free survival was 86% and 80% respectively. Combination of paclitaxel and cisplatin (17) or paclitaxel and vinorelbine (18) in order to further improve the effectiveness was met with higher toxicity and is not recommended now. Geara *et al.* (19) reported results of randomized trial comparing weekly cisplatin (40 mg/m^2) to paclitaxel (50 mg/m^2) concomitant with radiotherapy in LACC. Five-year overall survival was 54% with cisplatin *vs.* 43% with paclitaxel and the difference was non-significant.

Topoisomerase based regimens

Extrapolating from the benefit of combination of topotecan and cisplatin in metastatic and recurrent cervical carcinoma, Gatcliffe *et al.* (20) studied the role of this combination for radiosensitization in radical treatment of locally advanced cervical carcinoma. A weekly dose of 30 mg/m^2 of cisplatin and 2 mg/m^2 of topotecan were found to be tolerable and feasible with acceptable toxicity. In another study by Rose *et al.* (21), the tolerable doe levels were found to be 30 mg/m^2 of cisplatin and 0.5 mg/m^2 of topotecan. Fabbro *et al.* (22) defined the phase II dose of another topoisomerase inhibitor (Irinotecan) concomitant with cisplatin and radiotherapy. The doses suggested were cisplatin 20 mg/m^2 and irinotecan 35 mg/m^2 weekly. These studies have reported feasibility and have defined drug doses for these regimens. Response rates have ranged from 70–90% and survival outcomes have not been reported elaborately.

Gemcitabine based regimens

Zarbá *et al.* (23) showed encouraging complete response rates of 88.8% with concurrent cisplatin and gemcitabine with an acceptable toxicity (grade 3/4) rate of <20%. Drawing from these results, a phase III trial (24) evaluated the role of concurrent cisplatin plus gemcitabine *vs.* standard cisplatin based CCRT. The experimental arm also used 2 cycles of adjuvant chemotherapy with the same drug combination. The authors reported a superior overall survival (HR, 0.68; 95% CI, 0.49–0.95; P=0.0224) in the intervention group which came at the cost of overwhelming

grade 3/4 toxicity of 71.9% compared with 23.9% in the standard arm. The results of this study are unique in a way that the combination has shown survival advantage over the 'gold standard' of weekly cisplatin regimen. However, it remains unclear whether the benefit came from the novel chemo-radiotherapy combination or the addition of adjuvant chemotherapy.

Summary and future directions

Concurrent chemo-radiation with weekly cisplatin remains the gold standard as of now for LACC. The following drug combination and regimens needs to be tested against weekly cisplatin in well designed phase III trials for better defining their role as well as optimization of existing CCRT protocol:

- Concurrent gemcitabine and cisplatin;
- Concurrent paclitaxel with or without platinum;
- Concurrent carboplatin in subset of patients;
- Concurrent nedaplatin with or without taxane;
- Concurrent topotecan/irinotecan with or without platinum.

Molecular targeted and other novel agents with CCRT regimens

Agents tried in phase I/II studies

Commensurate with use of molecular targeted agents in other cancers, several drugs and agents are being evaluated for LACC; however, most of these are for metastatic and refractory cases. Limited studies have evaluated the incorporation of these in the radical CCRT protocols. Bevacizumab (25), erlotinib (26), cetuximab (27) and cyclo-oxygenase inhibitor celecoxib (28) have been all tried with CCRT regimens and found to be well tolerated and feasible in phase I/II studies.

Novel molecular pathway

Newer molecular pathways are being explored to find out the mechanism of resistance as well as targets of radiosensitization. Activation of PI3K/Akt/COX-2 pathway has been implicated in induction of resistance to radiation in cervical cancer HeLa cells (29). In a proof of principle study, it was later demonstrated that inhibition of phosphoinositide-3-kinase inhibition (by PI3K inhibitor-LY294002) leads to increased radio-sensitivity *in vivo* (30,31). The central mechanism of action of this drug was by inhibition of DNA-PK (DNA protein kinase) causing inhibition of DNA double stranded break repair (32). There is an urgent need of phase I/II trials for further elucidating and defining the role of PI3K inhibition in cervical cancer (33). Kunos *et al.* (34) investigated the role of M1, M2, M2b ribonucleotide reductase (RNR) subunit levels in 18 cervical cancer specimens and found over expression of M1 and M2b subunits to be associated with poor response to chemo-radiotherapy and to decreased disease free survival. In a subsequent study, the authors (35) used 3-aminopyridine-2-carboxaldehyde thiosemicarbazone (3-AP; an inhibitor of RNR) along with cisplatin and concurrent radiation in 22 patients of LACC. The combination was very well tolerated with clinical response of 96%. The encouraging results needs to further validated in randomized trial before clinical applicability.

Non-cytotoxic agents as radiosensitizers

Some of the drugs routinely used for other diseases have been found to have molecular signaling pathways which could be harnessed in cervical carcinoma. Hydralazine (36) (an anti-hypertensive agent) and magnesium valproate (37) (an anti-epileptic agent) has been found to be effective modifiers of radiation and are well tolerated with CCRT. troglitazone (a peroxisome proliferator-activated receptor agonist and anti-diabetic agent) has been found to increase radiation sensitivity of cervical cancer cells (HeLa cell lines) via G1 arrest (38). Pentoxifylline (a methylxantine drug used for circulatory disease) have been found to increase sensitivity of cervical cancer cells to cisplatin induced damage by inhibition of NF-κB pathway (39). Epigenetic modification is yet another way of potentiating the cytotoxicity as well as radiosensitivity of CCRT regimens. This may require further testing *in vivo* studies as well as phase I testing before reaching at any further conclusions.

Human papilloma virus (HPV) and radio-therapeutic outcomes

HPV infection is associated with >90% of the cervical carcinoma and HPV 16/18 accounts for >70% of all cervical cancers worldwide (40). Recent studies have suggested increased radiosensitivity of HPV related head neck cancers (accounting for 5–20% of all head and neck cancers) to

radiotherapy and chemotherapy and several strategies and trials towards de-escalation of treatment intensity in these subset of patients (41). A similar trend although premature is emerging for cervical carcinoma as well. Patients with high HPV titers at baseline (>1,000 relative light units) showed higher complete response rates as well as better overall survival as compared to those with low titers in the study by Datta *et al.* (42,43). A reduction of these values to 99.5% of the baseline values also predicted better survival in this study (42) and persistence of HPV infection leads to increased recurrence rates (43,44). HPV-16 associated oncoproteins E6 and E7 could also be potential targets of therapy. Sima *et al.* (45) showed increased apoptosis and senescence of transfected cervical carcinoma cells after treatment with antisense RNA and this approach needs further testing.

Summary and future directions

The landscape of combination of molecular targeting with CCRT regimen is rapidly evolving. The following warrants further research in this regard:

- Phase III studies of bevacizumab/erlotinib/celecoxib/cetuximab with CCRT;
- Phase I/II studies of PI3K inhibitor, RNR inhibitor, pentoxifylline and hydralazine with CCRT;
- HPV titer adapted treatment protocols (intensification for patients with less reduction of titers after CCRT).

Local therapies in combination with CTRT regimens

Hyperthermia and CTRT regimens

Combination of radiotherapy with hyperthermia remains a controversial and debated topic. Different mechanism of actions and toxicity profiles prompted interest in combining the two treatment modalities. Studies in other tumor sites like glioblastoma multiforme (46) and esophageal cancers (47) demonstrated improvement in local response rates and survival when thermo-radiotherapy was compared to radiotherapy alone. Results of this strategy is inconclusive for carcinoma cervix; while a randomized (48) International Atomic Energy Agency (IAEA) study failed to show benefit of thermo-radiotherapy over radiotherapy alone, other studies showed improvement in both local control as well as overall survival (49,50). A Cochrane analysis (51) based on the present available evidence suggested a benefit of thermo-radiotherapy approach over radiotherapy in terms of local control as well as overall survival without increase in grade 3 to 4 toxicity. One limitation of the older studies was the available device for the delivery of hyperthermia (48) and newer methods of catheter based ultrasound devices (52) may help in better and more conformal delivery of hyperthermia and thus further improving the therapeutic ratio. Despite the scientific rationale and proven results of hyperthermia, non-availability of the facility has restricted its use to limited number of centres worldwide. Time has also become ripe to propose trial designs comparing thermo-radiotherapy to chemo-radiotherapy in locally advanced cervical carcinoma.

Direct local delivery of agents

Direct local delivery of the radiation source, chemotherapeutic or targeted agents appear to be an innovative and novel method of cytotoxicity, particularly in cervix where local boost plays a vital role in the management. However, these methods have several challenges viz. unpredictable and sometimes high systemic absorption of locally delivered drugs, diffusion of the agents outside the interstitial spaces of tumor, backflow of the agents etc. Kim *et al.* (53) recently published their report on the use of micron-size radiotherapy source using a temperature sensitive hydrogel (RT-GEL). This consists of In-111 mixed with RT-GEL. Once injected in to the tumor, the solution converts in to a gel and is retained locally in the tumor tissue and delivers local radiation from the In-111 source. They also demonstrated no backflow with this technique, minimal systemic absorption and demonstratable cytotoxic effect on human breast tumor cells in animal models as compared to the control of In-111 admixed with saline. The initial results appear promising and definitely deserve testing in cervical cancer cells as well. Hodge *et al.* (54) reported local delivery of gemcitabine in patients with gynecological malignancy using a novel cervical delivery device (CerviPrep^{TM}). Cervical tissue, samples from the uterine vein as well as plasma was collected from 17 patients undergoing hysterectomy and they detected pharmacologically relevant concentration of gemcitabine in the cervical tissue. Even though concentrations of gemcitabine alone might not be enough for radio-sensitizing effect, combining this with low doses of cisplatin might be a step towards optimal radio-sensitization effect along with minimal systemic toxicity.

Nano-medicines as radio-sensitizing strategy

Gold nano-particles (GNPs) have been found to cause radiosensitization with kilovoltage (kV) radiation (55). The effect has predominantly been dedicated to increased photon absorption in high Z material and dominant role of photoelectric effect at kV radiation. Monte Carlo studies predicted less radiosensitization effect of GNP in the megavoltage (MV) range (56). However, the predictions are far from simple and assume only physical interaction of radiation with GNPs. Recent studies have found out additional mechanism of cytotoxicity like reactive oxygen species mediated, arrest of cytokinesis, apoptosis, inhibition of DNA repair etc. (57,58). Jain *et al.* (59) in their study on breast cancer cells demonstrated radiation sensitizer enhancement ratio of 1.29 and 1.16 respectively with 6 and 15 MV radiation respectively. Higher concentration of GNPs may be required in order to achieve higher dose enhancement factors; however this may come at the cost of increased toxicities. Combination of colloid GNPs with chemotherapeutic agents may be a novel mode of radiosensitization and needs testing in clinical trials. In fact, GNPs have already entered phase I trials in advanced cancer patients. Libutti *et al.* (60) reported results of pharmacokinetics study of CYT-6091 (constructed by combining recombinant human tumor necrosis factor alpha and thiolyated polyethylene glycol to the surface of colloidal GNPs) and found this nano-medicine to be well tolerated without serious adverse events.

Summary and future directions

The combination of local therapy with CCRT regimen appears promising. Although the results are premature, further testing definitely holds a ray of hope.

- Phase III trials evaluating thermo-radiotherapy to CCRT;
- Phase I/II studies of local delivery of cytotoxic agents in combination with low systemic dose of concurrent chemotherapy;
- *In-vitro*, *In-vivo* and cell line studies on application of nano-medicine with CCRT.

Palliation with CTRT regimens

Hypofractionated radiotherapy has been used for palliation of symptoms in locally advanced cervical carcinoma. A systemic review (61) in 2011 suggested paucity of existing literature on the optimal fractionation schedule for the same and need of future trials. Even in absence of level I evidence, most centres would prefer a fractionation schedule of 20–30 Gray in 5–10 fractions over 1–2 weeks (62). Radiation Therapy Oncology Group (RTOG) adopted a 10 Gray monthly dose with misonidazole in a quest to achieve a convenient and superior palliation (63), the study however was terminated in view of severe late gastrointestinal complications. There is an unmet need of research for this subset of patients. Study by Lagrange *et al.* (64) seems interesting in this regard; the authors evaluated the role of short infusion of 5 mg cisplatin for 5 consecutive days concomitant with radiation and found tumoral concentration of platinum to be in the range of radio-sensitization. Combining low daily dose of cisplatin with modest doses of radiation (20-25 Gray) may be an effective method of achieving palliation.

Table 1 summarizes the present status and future research directions on the use of novel agents and treatment techniques.

Conclusions

A number of approaches have appeared; initially as ripples and later as large promising waves for optimization of CCRT protocols in the management of carcinoma of uterine cervix. While many of these are in preliminary phases of investigations, some of these warrant immediate testing in phase III randomized trials. Molecular targeted agents, local delivery of cytotoxic agents and nano-medicines may become the frontline of management in the times to come and a more intricate co-ordination of translational and clinical research may bring overwhelming results. The enthusiasm and optimism of these novel agents and treatment techniques must be weighed against the widespread applicability particularly in resource constraint setting. Future studies should also focus on quality of life issues and cost-effectiveness analysis of these novel interventions. Nevertheless, the time perhaps has arrived for a breakthrough in the stagnant outcomes of carcinoma cervix with these preliminary and immature yet promising approaches.

Table 1 Summarizes the present status and future research directions on the use of novel agents and treatment techniques

Treatment modalities	Current perspective	Future research
Platinum based CCRT regimens	Weekly cisplatin remains the treatment of choice	Promising results with nedaplatin and gemcitabine; paclitaxel, topotecan/irinotecan needs further studies
Molecular targeted agents based CCRT regimens	Bevacizumab, erlotinib and cetuximab based regimens well tolerated and feasible: Needs phase III studies	PI3K and RNR inhibitors merit further studies
Hyperthermia	Inconclusive results from the existing trials. May have benefit as compared to radiotherapy alone	Need of well-designed studies comparing thermo-radiotherapy to CCRT
Direct local delivery of chemotherapeutic agents	Role not established in current practice	Combination of local delivery of chemotherapy along with low doses of systemic concurrent chemotherapy appears promising and needs evaluation
Nano-medicine as radiosensitizers	Preliminary results available and role not clear at the present time	Urgent need of translational research to further assess the role of these agents

CCRT, concurrent chemo-radiotherapy; PI3K, phosphoinositide-3-kinase; RNR, ribonucleotide reductase.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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