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Neo-adjuvant platinum-based chemotherapy followed by chemoradiation and radical surgery in locally advanced cervical cancer (Lacc) patients: A phase II study

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ABSTRACT

Purpose: The aim of this Phase II, non-randomized study was to assess activity and safety of neoadjuvant chemotherapy (NACT) before chemoradiation (CT/RT) followed by radical surgery (RS) in locally advanced cervical cancer (LACC) patients.

Methods and materials: The primary end point was rate of pathologic complete response (pCR). FIGO Stage IB2-IVA patients were administered NACT chemotherapy (paclitaxel 80 mg/m^2, carboplatin AUC 2), for 6 weeks, followed by Intensity Modulated Radiotherapy plus simultaneous boost (total dose of 50.4 Gy to CTV1, and 39.6 Gy to CTV2). Clinical response was assessed according to RECIST criteria. Responsive patients were triaged to RS. The regimen would be considered active if >20 pCRs were registered in 39 patients.

Results: 45 patients were enrolled into the study; 25 patients (55.5%) were FIGO stage IIB, 9 cases (20.0%) had stage III disease. At work up, pelvic lymph node involvement was documented in 38 (84.4%) patients; pCR was documented in 18 out of 40 patients (45.0%). Grade 3–4 hematological toxicity after NACT occurred in 4 patients; CT/RT associated grade 3 toxicity was found in 7 patients. Early and late post-operative complications were detected in 16, and 11 cases, respectively. Three-year PFS and OS were 66.0% and 86.0%, respectively.

Conclusions: NACT followed by CT/RT by IMRT and RS, is feasible and safe; failure to achieve the primary endpoint has to be recognized; however, enrollment of a higher rate of poor prognosis patients compared to historical data used to calculate sample size, could have resulted in reduced activity.

Introduction

Exclusive chemoradiation (CT/RT) has been representing since 1999 the standard treatment for locally advanced cervical cancer (LACC) patients, with an absolute 5-yr disease free survival (DFS) benefit of 8%, and an absolute 5-yr overall survival (OS) benefit of 6% compared to radiotherapy [1,2]. Moreover, very recent data from phase III randomized studies demonstrated the superiority of exclusive CT/RT compared to radiotherapy only in stage IIIB patients [3], and neo-adjuvant chemotherapy (NACT) plus surgery in stage IB2-II B patients [4].

Data from the Cochrane meta-analysis and other studies emphasized the potential role of chemotherapy administration

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after exclusive CT/RT, despite these suggestions cannot be considered as conclusive due to the limitations in terms of sample size, study design, and relatively short follow up [4–6]; in this context, the *"OUTBACK"* phase III randomized trial (NCT01414608, www.clinicaltrials.gov) has been set up to assess the role of adjuvant chemotherapy with cisplatin and paclitaxel after CT/RT *versus* CT/RT alone in the primary treatment of stage IB1 with positive lymph nodes, and stage IB2-IVA patients. In addition, administration of chemotherapy before CT/RT has been also taken into account in several retrospective and prospective studies [7–9], based on the rationale that neo-adjuvant chemotherapy (NACT), often administered on a weekly basis, could eradicate micro-metastatic distant disease, and reduce local tumor bulk, thus potentiating CT/RT activity. Finally, the possibility to fasten the start of treatment, especially in symptomatic patients, while waiting for radiation treatment planning, should not be underestimated. Indeed, the ongoing *INTERLACE* Phase III randomized study (NCT01566240, www.nih/clinicaltrials.gov) is testing the efficacy of carboplatin/paclitaxel followed by CT/RT compared to the current standard in patients affected by stage IB1 disease with metastatic lymph nodes, and stage IB2-IVA.

In the last 20 years, we have been managing LACC patients with preoperative CT/RT followed by radical surgery [10–12], a strategy also investigated by several groups, worldwide [13–15]; in addition, the adoption of completion surgery as a valid alternative to utero-vaginal brachytherapy is gaining wider and wider acceptance in low income countries where resources, in terms of radiotherapy facilities, and especially brachytherapy equipment, remain limited [16].

Here, we report the results of a Phase II, non-randomized study aimed at assessing the activity of neo-adjuvant platinum based chemotherapy before CT/RT followed by radical surgery in LACC patients. Details about acute and late toxicity associated with chemotherapy, and chemoradiation as well as rate and pattern of surgery related complications have been also analyzed.

Methods and materials

Study design and end-points

This prospective, non-randomized phase II study was aimed at assessing the activity of neo-adjuvant platinum based chemotherapy before CT/RT followed by radical surgery in LACC patients (FIGO stage IB2-IVA).

Primary end point was represented by rate of pathologically assessed complete response according to the intention-to-treat analysis; secondary end-points were progression-free survival (PFS), overall survival (OS), acute and late toxicity associated with chemotherapy, and chemoradiation, as well as rate and pattern of surgery related complications.

Eligibility

Patients with Stage IB2-IVA cervical cancer were evaluated for enrollment into the study by our institutional Tumor Board including Gynecologic Oncologists and Radiation Oncologists. The trial was approved by the local Ethics Committee and Institutional Review Board (P/2025/CE14), and all patients signed a written informed consent agreeing to be submitted to all the procedures described, and for their data to be collected.

Inclusion criteria were: biopsy-proven carcinoma of the cervix (any histotype), no evidence of distant disease, age $\leq$75 years, no previous treatment, ECOG performance status 0–1, adequate bone marrow function (WBC >3000/mm^3, platelets >120,000/mm^3), adequate renal function (blood urea nitrogen <25 mg/dl, creatinine <1.5 mg/dl), normal liver function (bilirubin <2 mg/dl), no prior cancer other than basal cell carcinoma. Exclusion criteria were as follows: previous or concurrent malignancies at other sites with the exception of basal or squamous cell carcinoma of the skin, uncontrolled severe infection and/or medical problems unrelated to malignancy which would limit full compliance with the study or expose the patient to extreme risk.

Pre-treatment work up included collection of medical history, clinical examination, abdomino-pelvic MRI, and PET/CT scan in order to exclude cases with distant sites of disease; cystoscopy and proctoscopy were carried out in case of clinical suspicion of bladder and/or rectum invasion.

Neo-adjuvant chemotherapy

Neo-adjuvant chemotherapy was administered for 6 consecutive weeks, and included paclitaxel (80 mg/m^2, 1 h infusion), and carboplatin (AUC 2, 1 h infusion).

Hematological toxicity was managed as follows: none of the drugs would be administered if neutrophils <1000/mm^3 or platelets <100,000/mm^3 were registered the day of treatment; if recovery did not occur the subsequent week, dose of drugs would be reduced by 15% (i.e. 68 mg/m^2 for paclitaxel and AUC 1.7 for carboplatin). In case of further toxicity, treatment administration would be stopped. Paclitaxel would be stopped in case of $\geq$G2 neurotoxicity. Monitoring of toxicity was planned on a weekly schedule.

Chemoradiotherapy and technique details

All patients underwent Computed Tomography (CT)-based planning in a supine position using combifix frame (Civco Inc., Orange City, Iowa, US). Patients received bowel preparation before simulation, and an empty rectum was required before CT simulation. To limit interfraction or intrafraction variability, a bladder-filling protocol was followed during CT simulation and subsequently before each treatment. Four-mm CT images were obtained from the upper border of the T12 vertebral body to 3 cm below the ischial tuberosity. Two clinical target volumes (CTV2 and CTV1) were identified and contoured on CT simulation scan, as follows: CTV2 included primary tumor and positive lymph nodes (GTV), the entire cervix, the parametria to the pelvic sidewall, vagina (entire or upper half according to involvement), the entire uterus, ovaries, obturator, external iliac, internal iliac, presacral (cranially to S2–S3 vertebras) and common iliac lymph nodes up to L4–L5 vertebras' junction. CTV1 corresponded to GTV plus 1.5-cm margin into the uterus and included the positive lymph nodes, if present. Planning target volumes (PTV2 and PTV1) were defined as clinical target volumes (CTV2 and CTV1) plus 8 mm. Organs at risk, including rectum, bladder, femoral heads and peritoneal bag were also contoured. The peritoneal bag was contoured from the axial slices situated 2 cm above the most superior slice containing the CTV and continued to its most inferior extent in the pelvis. Patients were treated with IMRT-SIB for a total dose of 50.4 Gy (2.3 Gy/fraction) to CTV1, and 39. 6Gy, (1.8 Gy/fraction) to CTV2 in 22 fractions. All PTVs were encompassed by a minimum of 95% of the prescribed dose. No more than 5% of any PTV received >105% of its prescribed dose. All plans consisted of five beams (6–15 MV) sliding windows IMRT; plans were generated with Eclipse™ treatment planning system and delivered by a TrueBeam® Linear Accelerator (Varian Medical System). For quality assurance through delivery, the set-up reproducibility was daily checked by on board kV images and weekly by cone beam assessment. During radiotherapy course, cisplatin (40 mg/m^2, 2-h intravenous infusion, once a week) was administered. Monitoring of toxicity was performed weekly.

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