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Phase II trial of neoadjuvant chemotherapy followed by chemoradiation in locally advanced cervical cancer☆

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HIGHLIGHTS

- NACT in cervical cancer patients did not improve ORR.
- Induction chemotherapy followed by CRT increased toxicity.
- NACT followed by CRT should be further explored in prospective trials.

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ABSTRACT

Objective. Cervical cancer is a global public health challenge. Since 1999, platin based chemoradiation (CRT) is the standard treatment for those patients with locally advanced disease. However, this population still has a dismal prognosis and, alternatives approaches such as adjuvant chemotherapy are controversial, especially because of increased toxicity. Neoadjuvant chemotherapy (NACT) could be an option for more intensive treatment with manageable toxicity.

Methods. A phase II, prospective, non-randomized trial was conducted at a reference center in Recife, Brazil. Locally advanced cervical cancer patients (Ib2–IVa) were treated with neoadjuvant cisplatin 35 mg/m^2 and gemcitabine 1000 mg/m^2 D1 and D8, for 2 cycles. Then, they received CRT (50.4 Gy) with weekly cisplatin 40 mg/m^2 followed by brachytherapy. Response rate (RR) and toxicity were the primary endpoints. Progression-free survival (PFS) and overall survival (OS) were secondary endpoints.

Results. Between Sep/2013 and Oct/2015, 50 patients were initiated on NACT and CRT. RR was 81% at the end of treatment. Hematological and gastrointestinal toxicity were most common. Grade 3/4 toxicity was 20% during NACT and 44% during CRT. Late adverse events were present in 20% of patients. PFS at 1 and 3-years were 73.4% (IC 58.7–83.6) and 53.9% (IC 36.9–68.3), respectively; and, OS at 1 and 3-years were 93.9% (IC 82.4–98.0) and 71.3% (IC 53.3–83.3), respectively.

Conclusion. In our hands NACT in locally advanced cervical cancer patients did not show a meaningful improvement in ORR. Nevertheless, we believe it should be further explored in prospective trials.

1. Introduction

Cervical cancer is a global public health challenge. Overall, it is now the fourth most common cause of cancer in women [1], with the burden of disease being in low- and middle-income countries where under-resourced health systems are unable to provide well-known effective

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prevention network. Furthermore, cervical cancer remains the third cause of death from malignant disease in women worldwide [1,2].

Although platin based chemoradiation (CRT) has been the standard treatment for patients with locally advanced disease since 1999 [3], the availability of radiotherapy and access to this type of treatment is limited in most of low- middle-income countries [4]. Delays in obtaining access to effective treatment lead to increased morbidity and mortality [5,6]. Bleeding, obstructive renal insufficiency and pain are possible complication that may develop while the patient awaits treatment. Furthermore, when all stages of the disease are evaluated together, the 5-year survival rate is below 60% in low income countries compared to 70% in high income nations [2].

Alternative approaches, although pursued over the years, remain controversial. In 2011, the addition of gemcitabine to CRT followed by adjuvant chemotherapy was associated with increased survival with limiting toxicity profile, which precluded its use in clinical practice [7]. This data raised questions about the role of additional chemotherapy in this setting.

Neoadjuvant chemotherapy (NACT) plays a yet unproved role in cervical cancer treatment, particularly when followed by CRT, where data is scarce [8]. The rationale for induction chemotherapy is that it may reduce tumor volume while controlling micrometastatic disease. Therefore, it could be considered as an alternative approach to adjuvant chemotherapy, with a better toxicity profile, while hastening an effective treatment for those patients. In this trial, we evaluated efficacy and toxicity of NACT followed by platin based CRT in locally advanced cervical cancer (LACC) patients.

2. Methods

2.1. Patient selection

A phase II, non-randomized prospective trial was conducted at reference hospital (the Instituto de Medicina Integral Professor Fernando Figueira - IMIP) located in a low-income area at Recife, Brazil. Eligibility criteria consisted of patients with newly diagnosed LACC, FIGO [9] stage IB2–IVa squamous cell carcinoma who were suitable for CRT. Patients were required to have age 18 to 70, performance status 0–2 with no significant renal, hepatic or hematological impairment. Patients were excluded from the study if they had adenocarcinoma, adenosquamous or small cell carcinoma, a history of another cancer, pregnancy, previous oncologic treatment such as surgery, radiation or chemotherapy and contraindication to CRT.

2.2. Treatment schedule

LACC patients (stage Ib2–IVa) were treated with neoadjuvant cisplatin 35 mg/m^2 administered by intravenous infusion over 1 h followed by gemcitabine 1000 mg/m^2 intravenously infusion administered over 30–60 min on days 1 and 8, for 2 cycles with an interval of 21 days between then. Dexamethasone and ondansetron were given as premedication. Then, patients received standard treatment with CRT. Radiotherapy consisted of 50.4 Gy to the entire pelvic region in 28 fractions of 1.8 Gy/d, five days a week, over six weeks. A standard four-field box technique was administered using a linear accelerator 6 MV of energy. Cisplatin 40 mg/m^2 was administered by intravenous infusion over 1 h was administered weekly during radiation therapy. After pelvic radiation, high dose rate (HDR) intracavitary brachytherapy (BCT) of 28 Gy was applied to point A (7 Gy, 4 fractions). A boost f 10 Gy was applied in those patients for whom BCT was not suitable. Fig. 1 summarizes study design.

Gemcitabine dose was adjusted according to hematologic toxicity. Dose was reduced by 25% if neutrophil count was 1000 to 1500/ml and/or platelets were 100.000–75.000; dose was reduced by 50% if neutrophil count was 800–999 and platelets were ≥50.000. If neutrophil count was <800 or platelets <50.000, gemcitabine was discontinued until hematologic improvement to grade 1 was achieved.

2.3. Assessment

At baseline, all patients were physically examined by a gynecological oncologist. They were submitted to pelvic magnetic resonance imaging (MRI), positron emission tomography (PET-CT), pregnancy test, full blood counts and biochemistry. During treatment, patients had oncologist visits before each day of chemotherapy during NACT and weekly visits during CRT. Gynecological oncologist examination was repeated after NACT, a month after BCT and again 3 months after treatment. PET-CT and pelvic MRI were repeated at least 3 months after treatment, when response rate was evaluated. Patients were followed up every 3 months during first two years and every six months thereafter.

2.4. Statistical analysis

Considering a response rate (RR) of 85% for CRT alone and 95% for CRT plus additional chemotherapy, based on Dueñas-Gonzalez phase III trial [7], we calculated a need of 49 patients, with 80% power and 5% significance (one-sided). Recruitment started in September 2013 and finished in December 2015. The trial was conducted according to International Conference on Harmonization Good Clinical Practice Guideline. All patients signed an informed consent form. The study protocol was approved by local Ethics Committee number 14120713.4.0000.5201 and was registered in *ClinicalTrial.gov* as NCT02309658.

Response rate and toxicity were primary endpoints. Response was assessed in accordance with the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) [10]. Toxicity was graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Adverse events occurring after 6 months from the end of treatment were considered late toxicity. Survival was a secondary endpoint. Progression-free survival (PFS) was calculated from

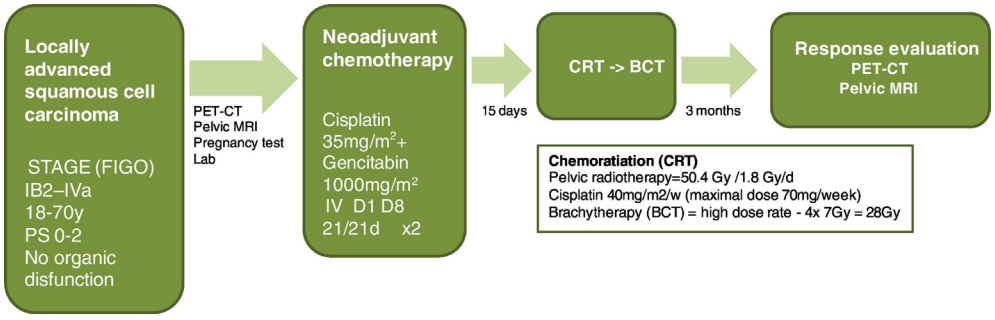

Fig. 1. Study design. FIGO = International Federation of Gynecology and Obstetrics; PS = performance status; PET-CT = positron emission tomography-computed tomography; MRI = magnetic resonance imaging; Lab = laboratory tests.

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