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Review article

Advancing clinical research globally: Cervical cancer research network from Mexico

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ABSTRACT

Cervical cancer is the fourth most common cancer in women with 85% of the mortality burden occurring in less-developed regions of the world. The Cervix Cancer Research Network (CCRN) was founded by the Gynecologic Cancer InterGroup (GCIG) with a mission to improve outcomes in cervix cancer by increasing access to high-quality clinical trials worldwide, with particular attention to less-developed, underrepresented sites. The CCRN held its second international educational symposium in Mexico City with ninety participants from fifteen Latin America countries in January 2017. The purpose of this symposium was to advance knowledge in cervix cancer therapy, promote recruitment to CCRN clinical trials, and to identify relevant future CCRN clinical trial concepts that could improve global care standards for women with cervical cancer.

1. Introduction

Cervical cancer is the fourth most common cancer in women worldwide with > 85% of cervical cancer deaths occurring in less-developed regions of the world, corresponding to an 18-fold disparity in mortality rates (International Agency for Research on Cancer WHO, 2018). The Gynecologic Cancer InterGroup (GCIG) is a non-profit collaborative network of international and national research groups aiming to promote and facilitate high-quality clinical trials in order to improve outcomes for women with cervical cancer and other gynecologic malignancies. The Cervix Cancer Research Network (CCRN) was founded by the GCIG to facilitate the mission to improve global cervical cancer outcomes by increasing access to high-quality cervix cancer clinical trials within regions around the world not currently represented by a GCIG member cooperative group (Gaffney et al., 2015). The inaugural international CCRN symposium held in Thailand in January 2016 encouraged recruitment to clinical trials in Southeast Asia, a region encompassing nearly half of the cervical cancer incidence and mortality in the less-developed world (Gaffney et al., 2016). In January 2017, the CCRN held its second annual symposium in Mexico City with 90 participants representing 15 countries across Latin America. The third annual CCRN symposium was held in Bucharest in January 2018,

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with attention to advancing cervix cancer care in Eastern Europe. The focus of these CCRN education symposiums is to provide a global perspective of treatment modalities, controversies, and trending subjects in the management of cervical cancer. The following report summarizes the proceedings of the 2017 annual symposium in Mexico City and highlights the ongoing work of the CCRN as it relates to Latin America in enhancing standards of care, improving clinical outcomes, and fostering access to clinical trials.

Approximately 15% of deaths from cervical cancer in the less-developed world occur in Latin America, corresponding to a mortality rate of about 28,000 per year (International Agency for Research on Cancer WHO, 2018). The necessary infrastructure, expertise, and funding required to deliver modern cervical cancer treatments remain significant barriers to executing clinical trials in Latin America. In Mexico, where only 15% of cervical cancers are detected at an early stage, a human papillomavirus (HPV) vaccination campaign was instituted in 2008 for girls 9–16 years old. Despite these efforts, the overall disease burden, treatment outcomes, and the numbers of women seeking care are still lagging when compared to more developed countries.

In addition to being potentially preventable with HPV vaccination and screening, cervical cancer has also become increasingly curable with contemporary chemoradiotherapy due to high rates of radiosensitivity and improved survival with concurrent cisplatin chemotherapy (Chemoradiotherapy for Cervical Cancer Meta-Analysis C, 2008). However, cervical cancer remains a leading cause of cancer death among women in countries with a low Human Development Index – a measure of socioeconomic development accounting for levels of education, life expectancy, and income (Atun et al., 2015). On average, only one radiotherapy machine is available for every 2 million people in Mexico, ranking among the lowest densities of radiotherapy access in Latin America (Pinillos et al., 2017). A Quality Assurance Team for Radiation Oncology (QUATRO) audit of 12 Latin American radiotherapy centers from 2008 to 2013 found local training programs and research activity to be scarce, in addition to discovering that 25% of centers lacked gynecologic brachytherapy and did not meet minimum infrastructure requirements (Rosenblatt et al., 2015).

In a survey of 47 Latin American participants at the 2017 CCRN symposium, 38% reported insufficient numbers of radiation machines as the most common barrier to the treatment of cervical cancer with curative intent. Radiating Hope, a nonprofit volunteer-run organization seeking to improve global access to modern radiotherapy technologies, is working to increase Latin American access to radiotherapy through established avenues in Guatemala, Honduras, Panama, Peru, and Chile. Despite these efforts, many additional barriers to treatment were cited, including presentation with disease too advanced (77%), long wait times (40%), and social issues (33%), emphasizing the complex challenges faced by Latin American providers. Approximately two-thirds of participants in the survey had never enrolled a cervical cancer patient on a clinical trial. The most commonly cited barriers were the lack of available open trials (66%), limited funding (58%), limited research support staff (39%), and lack of infrastructure (34%). Survey responders represented a balanced, multidisciplinary group from across Latin America composed of gynecologist oncologists (38%), medical oncologists (19%), radiation oncologists (34%), and support staff (9%). To address these multifactorial challenges faced by Latin American healthcare providers, the CCRN is committed to expanding access to externally-funded high-quality clinical trials in Latin America. By supporting access to ongoing and future CCRN clinical trials through the development of new CCRN accredited sites in low- and middle-income countries, the CCRN aims to advance knowledge in cervical cancer therapy and to improve care standards throughout the world.

2. CCRN clinical trials

As of 2017, 29 cooperative research groups comprised the membership of the GCIG, including 8 in North America, 15 in Europe, 5 in Asia, and 1 in Australia/New Zealand. Currently, there are no GCIG member groups solely based in South America, because GCIG membership is based on a pre-existing established national or multi-national cooperative group eligible to join the GCIG. At the CCRN symposium in Mexico City, there was significant interest from different centers in working to establish national research groups with a view to joining GCIG. Participation in CCRN was seen as an attractive initial step towards this goal. Sites without GCIG representation that are interested in obtaining CCRN accreditation must comply with some basic radiation and research requirements, including completion of a radiologic/physics prequalifying questionnaire (courtesy of IROC, Houston, TX) and participation in a radiotherapy beam measurement program with thermoluminescence dosimeters or optically stimulated luminescence dosimeters every two years. Site reviews are then undertaken by a GCIG team to ensure treatment and research facilities have the necessary framework in place to ensure compliance with standards as dictated by the International Council for Harmonisation of Technical Requirements for Human Use Good Clinical Practice (ICH GCP). Continued quality assurance is performed according to individual clinical trial specifications.

Several publically funded, low-cost GCIG clinical trials are currently active at CCRN accredited sites (Table 1). The CCRN trial with the highest number of CCRN accruals to date is the Tri-weekly Administration of Cisplatin in Locally Advanced Cervical Cancer (TACO) Trial, developed by investigators from the Korean Gynecologic Oncology Group (KGOG) and Thai Cooperative Group. Based upon promising phase II data showing improved survival with cisplatin dosing every three weeks, eligible locally advanced cervical cancer patients receiving concurrent chemoradiation in this phase III study are randomized between 6 cycles of standard 40 mg/m^2 weekly cisplatin versus 3 cycles of 75 mg/m^2 cisplatin every 3 weeks (Ryu et al., 2011). If confirmed to improve overall survival, the administration of cisplatin every 3 weeks could result in significant cost savings for health systems, thereby improving outcomes while also increasing accessibility for patients. This trial remains open to accrual and has accrued patients from Asia.

To address high rates of distant failure in advanced cervical cancer

Table 1
Currently active CCRN clinical trials as of January 1, 2018.

Trial name	Phase	Study question	Status	Countries participating
TACO	III	Tri-weekly versus weekly cisplatin concurrent with radiotherapy	Open	South Korea, Thailand, Vietnam, China
INTERLACE	III	Weekly induction carboplatin paclitaxel chemotherapy followed by standard chemoradiation versus standard chemoradiation	Open	United Kingdom, Mexico, Italy
OUTBACK	III	Standard chemoradiation with or without adjuvant carboplatin paclitaxel chemotherapy	Closed, met accrual June 2017	Australia, Canada, China, New Zealand, Saudi Arabia, Singapore, United States
SHAPE	III	Simple versus radical hysterectomy with pelvic node dissection in low-risk early stage cervical cancer	Open	Canada, France, United Kingdom, Belgium, Netherlands, Austria, South Korea, Ireland, China, Russia, Germany
Hypofractionation trial	II	Standard chemoradiation 50 Gy in 25 fractions versus hypofractionated chemoradiation 40 Gy in 16 fractions, followed by surgery	Open	Mexico, Honduras