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Review article

Clinical trials in low and middle-income countries — Successes and challenges

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ABSTRACT

Gynecologic malignancies affect women in low and middle-income countries (LMICs) at equal or higher rates compared to high income countries (HICs), yet practice guidelines based on clinical trials performed in HICs do not routinely account for resource disparities between these regions. There is a need and growing interest for executing clinical trials in LMICs. This has led to the creation of multinational cooperative groups and the initiation of several ongoing clinical trials in Mexico, China, and Korea. In this article we describe the challenges involved in initiating clinical trials in LMICs, review current efforts within surgical, medical, and radiation oncology, and introduce high priority topics for future research.

Contents

1. Introduction

Gynecologic malignancies such as breast, cervical, and uterine cancers represent the first, third, and fifth most common cancers in women globally (Ferlay et al., 2015). Together, these malignancies account for 24% of all cancer deaths in women (Ferlay et al., 2015). Gynecologic cancers also disproportionately affect women in low and

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middle-income countries (LMICs). Less developed regions of the world carry 84% of the burden of cervical cancer diagnoses and 87% of cervical cancer mortality yet frequently lack the necessary resources to optimize diagnosis and treatment (Ferlay et al., 2015). Acknowledging these disparities, professional societies and cooperative groups have sought to stratify treatment guidelines by resource availability (e.g. National Comprehensive Cancer Network (NCCN) Framework Guidelines and American Society of Clinical Oncology (ASCO) Resource-Stratified Clinical Practice Guidelines) (Carlson et al., 2016; Chuang et al., 2016). However, best practices within LMICs should ideally be established through clinical trial evidence.

In resource-limited populations, numerous barriers exist to prevent clinical trial design and execution. Commonly cited examples are lack of infrastructure, heterogeneity of resource availability among countries, unfamiliarity with clinical trial regulations, cultural/ethical issues, and other legal constraints around data-sharing. The few examples of large-scale clinical trials conducted in LMICs for HIV/AIDS and cervical cancer screening serve as valuable models for clinical trial design for gynecologic malignancies (Sankaranarayanan et al., 2009; Campbell et al., 2012; Adefuye et al., 2013). Unfortunately, oncologic treatment requires the expertise of multidisciplinary physicians and ancillary staff as well as the accompanying operating room equipment, chemotherapeutics, imaging machines and/or radiation therapy (RT) machines that can add an additional, and potentially prohibitive, layer of expense.

Herein we describe the unique obstacles for clinical trial execution in gynecologic oncology in LMICs, review current efforts for trial design in surgical, medical, and radiation oncology, and introduce high priority topics for future research.

2. Existing obstacles for clinical trials in LMICs

Clinical trials in oncology have increased in parallel to increasing cancer prevalence in LMICs. In the recent past, conducting clinical trials in LMICs drastically curtailed costs and resulted in a transient increase in clinical trials. Many of these trials were unfortunately enabled by exploitation of ignorance, poverty, and poor awareness of the human subject rights and safety issues. For instance, in India, there was an initial surge in pharmaceutical clinical trials until 2010 and a sharp fall with decreasing trend subsequently (Chawan et al., 2015). Major concerns included poor quality of informed consent, poor quality of scientific and ethical review processes, sub-optimal regulatory processes for new drugs and clinical trials, inadequate protection of the patient's rights and compensation for trial-related injury and, more importantly, lack of post-trial population access to prohibitively expensive cancer drugs which were proven effective in LMIC settings (Shapiro and Meslin, 2001). Subsequent rapid amendments in regulations at frequent intervals related to patient rights, compensation, and timelines in India have resulted in loss of enthusiasm for both the investigator-initiated and industry-sponsored trials (Sirohi et al., 2014). Similarly, many other LMICs have their own laws, regulatory requirements, policies and guidelines for the conduct of clinical research, especially in regard to international multi-center collaborative trials. This not only complicates the conduct of collaborative trials, but also prevents the ability to address cancers with higher prevalence in LMICs.

Other obstacles include logistics, research relevancy and implementation issues (Saini et al., 2013; Dandekar et al., 2016; Seruga et al., 2014). Logistically, there are a paucity of facilities, trained human resources, expertise, capacity building and motivation for the conduct of research. Clinical trial execution in these settings would therefore need to identify a payer, whether governmental, non-governmental, sponsor, or other, who would be able to fund for these deficiencies. Clinical trials in LMICs may also be subject to completing research priorities. Funding for clinical trials may not prioritize conditions that are seen most frequently in LMICs due to decreased prevalence (and decreased estimated revenue) in HICs. Even if clinical trials could successfully demonstrate efficacy in LMICs, the ability to provide a plan for long term implementation of these interventions pose major challenges to global funding and ethics committees.

While not specific to conducting clinical trials, disparities in healthcare systems, social and cultural differences, reimbursement policies, and healthcare professional staffing are additional obstacles. Most patients have to assume the cost of their health care, including initial treatment and possible subsequent management of complications associated with treatment (White, 2015). In addition, competing local traditional treatment and the lack of patient education and support present as other major barriers for conducting clinical trials in LMICs (White, 2015). High-quality pathology and cancer registries are limited in LMICs. In sub-Saharan Africa, there is less than one pathologist per 500,000 persons (Adesina et al., 2013). Similar to the lack of pathologists, there are limited trained cancer surgeons. The number of surgeons is fewer than two per 100,000 persons (Lavy et al., 2011; Meara et al., 2016). These numbers are substantially lower than one pathologist per 15,000 and 35 surgeons per 100,000 persons in the United States. The ability to conduct clinical trials are hampered by the limited ability to provide cancer care in setting of limited human resources.

3. Current status of gynecological cancer clinical trials

The Gynecological Cancer InterGroup (GCIG) orchestrates many of the current trials in gynecological malignancies. The GCIG is an organization of international cooperative groups that perform gynecological cancer research. It is a nonprofit corporation that has structured governance, bylaws and standard operating procedures. GCIG aims to promote and facilitate high quality clinical trials in order to improve outcomes for women with gynecological cancer. GCIG was conceived in 1993 and formalized in 1997 and has 29 member groups including representation from North America, Europe, Asia and Australia. The GCIG has a number of standing committees including cervix, endometrial, ovarian, rare tumors and a dedicated committee to accomplish phase 2 trials. The group has been very effective and has a history of successful collaboration and completion of randomized phase III trials, consensus conferences, brainstorming (state-of-the-art) initiatives, publications and reviews. International participation in trials has enabled achievement of rapid recruitment and international credibility for the results. Current GCIG trials are looking at all aspects of gynecological cancer treatment including systemic, radiation and surgical questions. The group strongly supports the mission of providing access to relevant, high quality clinical trials in LMICs.

Table 1
Examples of clinical trials for gynecologic malignancies in low- and middle-income countries. RT = radiation therapy.

Trial	Design	Investigators
ConCerv	Cone biopsy or simple hysterectomy with or without pelvic node dissection in low-risk, early cervical cancer	Global Gynecologic Oncology Consortium
Interlace	Induction chemotherapy plus chemoradiation vs. chemoradiation in advanced cervical cancer	National Cancer Research Institute (NCRI), United Kingdom
Outback	Weekly cisplatin/RT vs. weekly cisplatin/RT followed by outback chemotherapy in advanced cervical cancer	Australia/New Zealand Gynecologic Oncology Group (ANZGOG) and the NRG Oncology Group, USA
Shape	Radical hysterectomy and pelvic node dissection vs. simple hysterectomy and pelvic node dissection in low-risk, early cervical cancer	National Cancer Institute of Canada (NCIC) Clinical Trials Group
TACO	Weekly cisplatin/RT vs. tri-weekly cisplatin/RT in advanced cervical cancer	Korean Gynecologic Oncology Group (KGOG) and Thai Cooperative Group