Gynecologic Oncology xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Review Article

Cervical cancer – State of the science: From angiogenesis blockade to checkpoint inhibition

Lindsey E. Minion, Krishnansu S. Tewari *

The Division of Gynecologic Oncology, University of California, Irvine, United States

HIGHLIGHTS

- The rationale to support the study of anti-angiogenesis therapy is described.
- The results of GOG protocol 240 are presented along with global aftermath.
- The thesis of immunologic tolerance manifestation in cervical cancer is developed.
- Studies of checkpoint inhibition in advanced cervical cancer are highlighted.

ARTICLE INFO

Article history:
Received 28 November 2017
Received in revised form 7 January 2018
Accepted 12 January 2018
Available online xxxx

Keywords:
Advanced cervical cancer
Metastatic cervical cancer
Recurrent cervical cancer
Anti-angiogenesis therapy
Bevacizumab
Checkpoint inhibitors

ABSTRACT

Vascular endothelial growth factor (VEGF) has emerged as a therapeutic target in several malignancies, including cervical cancer. Chemotherapy doublets combined with the fully humanized monoclonal antibody, bevacizumab, now constitute first-line therapy for women struggling with recurrent/metastatic cervical carcinoma. Regulatory approval for this indication was based on the phase III randomized trial, GOG 240, which demonstrated a statistically significant and clinically meaningful improvement in overall survival when bevacizumab was added to chemotherapy: 17.0 vs 13.3 months; HR 0.71; 98% CI, 0.54–0.95; p = .004. Incorporation of bevacizumab resulted in significant improvements in progression-free survival and response. These benefits were not accompanied by deterioration in quality of life. GOG 240 identified vaginal fistula as a new adverse event associated with bevacizumab use. All fistulas occurred in women who had received prior pelvic radiotherapy, and none resulted in emergency surgery, sepsis, or death. Final protocol-specified analysis demonstrated continued separation of the survival curves favoring VEGF inhibition: 16.8 vs 13.3 months; HR 0.77; 95% CI, 0.62–9.95; p = .007. Post-progression survival was not significantly different between the arms in GOG 240.

Moving forward, immunotherapy has now entered the clinical trial arena to address the high unmet clinical need for effective and tolerable second line therapies in this patient population. Targeting the programmed cell death 1/programmed death ligand 1 (PD-1/PD-L1) pathway using checkpoint inhibitors to break immunologic tolerance is promising. The immunologic landscape involving human papillomavirus-positive head and neck carcinoma and cutaneous squamous cell carcinoma can be informative when considering feasibility of checkpoint blockade in advanced cervical cancer. Phase II studies using anti-PD-1 molecules, nivolumab and pembrolizumab are ongoing, and GOG 3016, the first phase III randomized trial of a checkpoint inhibitor (cemiplimab) in cervical cancer, recently activated. Important considerations in attempts to inhibit the inhibitors include pseudoprogression and post-progression survival, abscopal effects, and immune-related adverse events, including endocrinopathies.

Abbreviations: PMH, past medical history; ROS, review of systems; WNL, within normal limits; C, cycle; BP, blood pressure; UTI, urinary tract infection; NIDDM, non-insulin-dependent diabetes mellitus.

* Corresponding author at: The Division of Gynecologic Oncology, University of California, Irvine, Department of Obstetrics & Gynecology, The City Tower, 333 City Blvd, West - Suite 1400, Orange, CA 92868, United States.
E-mail address: ktewari@uci.edu (K.S. Tewari).

https://doi.org/10.1016/j.ygyno.2018.01.009
0090-8258/

Contents

1. Introduction

During 2018, the American Cancer Society estimates that there will have been 13,240 new cases of cervical cancer and 4,170 deaths in the United States [1]. This is unacceptable given the availability of prophylactic human papillomavirus (HPV) vaccination and early detection of preinvasive disease via cytologic screening and/or high-risk HPV DNA testing. Worldwide, there is a disproportionate distribution of cases in resource poor settings without appropriate infrastructure to support screening programs. In 2012, cervical cancer rated as the fourth most common malignancy globally with 527,600 new cases [2,3].

In industrialized nations, invasive disease is often diagnosed during the prime years of a woman's life (median age 49), in the midst of their careers and/or with small children at home. This patient population is more likely to be immunodeficient, abuse tobacco, and be marginalized by society due to lower socio-economic status [4–7].

Early stage cancers (FIGO IB_1) may be treated by robotic radical hysterectomy with sentinel lymph node mapping and tailored adjuvant therapy. When future child-bearing is desired, fertility-preserving radical trachelectomy with lymphadenectomy may be appropriate in select cases (FIGO $IB_1 \leq 2$ cm). Locally advanced disease (FIGO IB_2-IVA) can be cured with chemoradiation plus high-dose-rate (HDR) brachytherapy. Women who experience post-radiotherapy isolated central recurrences may be rescued via pelvic exenteration, however, this indication is becoming less frequent following widespread adoption of chemoradiation protocols with more local failures being accompanied by distant metastases. The management of women with recurrent disease who are not candidates for pelvic exenteration and those who present with metastatic (FIGO stage IVB) disease has represented an unmet clinical need for decades.

2. Part one: what has gone before

From the 1980's to 2009 the National Cancer Institute's (NCI) Gynecologic Oncology Group (GOG) conducted eight phase III randomized trials evaluating cytotoxic chemotherapy for metastatic and recurrent cervical cancer [8–13]. Clinically meaningful improvements in survival remained elusive and with GOG protocol 204 the regimen of cisplatin (50 mg/m^2) plus paclitaxel (135 mg/m^2) emerged as standard of care [14]. Response rates were short-lived and patients experienced rapid deterioration of performance status (PS) and quality of life, with early death 7–12 months from diagnosis. Furthermore, with widespread adoption of cisplatin-based chemoradiation for locally advanced disease, there was concern for platinum resistance at recurrence, thus prompting a search for an active and tolerable non-platinum doublet [15]. Topotecan plus paclitaxel was selected based on preclinical studies suggesting synergy between topotecan and microtubule-interfering agents, and phase II data which demonstrated tolerability and activity in heavily pretreated women [16,17].

2.1. A rationale to target tumor angiogenesis

The NCI's Cancer Therapy and Evaluation Program (CTEP) permitted anti-angiogenesis therapy to also be studied based on clinical, pathologic, therapeutic, and molecular rationale. *Clinically*, aberrant vascular markings seen during colposcopic examination (punctuation, mosaicism, atypical vessels) in women with abnormal cervical cytology represent harbors of angiogenesis, suggesting that neovascularization is important early in pathogenesis. *Molecularly*, viral integration of oncogenic HPVs and expression of viral proteins E6 and E7 inhibit key

Please cite this article as: L.E. Minion, K.S. Tewari, Cervical cancer – State of the science: From angiogenesis blockade to checkpoint inhibition, Gynecol Oncol (2018), https://doi.org/10.1016/j.ygyno.2018.01.009