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Review Article

Management of the toxicities of common targeted therapeutics for gynecologic cancers

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HIGHLIGHTS

- Biologic agents have unique toxicity profiles to that of standard chemotherapeutics.
- Immunotherapy drugs cause autoimmune toxicities and require close monitoring.
- Thorough understanding and keen awareness of toxicities are key with targeted agents.

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ABSTRACT

As precision medicine has become a focus in oncology in recent years, many targeted and biologic agents are being used along with or in place of traditional cytotoxic chemotherapy. As these drugs have been developed and some have received FDA approval, we have gained substantial data about the adverse event profiles. However, the management and approach to the toxicities incurred and subsequent complications are often not well understood, especially for physicians who have a varied clinical practice. The purpose of this review is to provide an overview of the frequency and types of adverse events and appropriate management steps when prescribing modern targeted therapies for gynecologic cancers in the classes of anti-angiogenic agents, poly-ADP-ribose polymerase (PARP) inhibitors, and immunotherapy drugs.

Contents

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1. Introduction

Targeted therapies have become an attractive focus of research and drug development in recent years given the accumulation of toxicities and eventual development of resistance with continued use of conventional chemotherapy. Use of these agents requires balancing disease-related symptoms and emergence of treatment-related adverse events, particularly if the agent is not known to prolong overall survival. Many targeted therapies have a similar adverse events (AEs) profile as that seen with chemotherapy, but some agents have class-specific or unique toxicities not otherwise expected. It is important to consider priorities of individual patients to determine the risk-benefit ratio. For example, extension of progression free survival (PFS) may not be relevant if quality of life (QOL) is impaired. Herein we will review the indications, mechanisms of action, toxicities, and remedies for 3 classes of commonly used targeted therapeutics which have received United States Food and Drug Administration (US FDA) approval for gynecologic cancers: anti-angiogenic agents, PARP inhibitors, and immunotherapy.

2. Anti-angiogenic agents

Anti-angiogenic agents (AA) are a well-studied and widely used therapy for gynecologic cancers with multiple indications. These agents, while generally well tolerated, have unique AEs requiring attentive, timely, and proactive management.

2.1. Mechanisms of action and current indications

Currently there are two AA with FDA indications in gynecologic cancers, bevacizumab and pazopanib.

- Bevacizumab is a recombinant humanized monoclonal IgG1 antibody targeting vascular endothelial growth factor (VEGF). In gynecologic cancers, it has indications in cervical cancer and recurrent epithelial ovarian cancer (EOC; both platinum sensitive and resistant). For platinum sensitive EOC, bevacizumab approvals are based on the OCEANS trial and Gynecologic Oncology Group (GOG) 213 that tested adding bevacizumab to carboplatin based chemotherapy [1,2]. The approval in platinum resistant disease is based on the AURELIA trial which added bevacizumab to single agent chemotherapy versus chemotherapy alone [3]. GOG218 and ICON7 led to bevacizumab approval by the European Medicines Agency (EMA) when combined with carboplatin/paclitaxel in newly diagnosed advanced high risk EOC; this expanded indication is currently under FDA review [4,5]. The clinical trial GOG240 evaluated doublet chemotherapy with or without bevacizumab in advanced/ recurrent cervical cancer leading to FDA approval in this indication as well [6].
- Pazopanib is a tyrosine kinase inhibitor (TKI) targeting VEGFR-1, -2, and -3, platelet-derived growth factor receptor (PDGFR)-α and -β, fibroblast growth factor receptor (FGFR) -1 and -3, cytokine receptor (Kit), interleukin-2 receptor inducible T-cell kinase (Itk), leukocyte-specific protein tyrosine kinase (Lck), and transmembrane glycoprotein receptor tyrosine kinase (c-Fms). Pazopanib is indicated for use as a single agent in patients with advanced soft tissue sarcomas who have received prior anthracycline chemotherapy based on the PALETTE phase III study [7].

2.2. Prevalence and severity of AA AEs

Table 1 details the incidence of AEs as organized by organ system with administration of AA.

2.2.1. Cardiovascular

The use of AA is widely associated with cardiovascular AEs including hypertension (HTN), left ventricular dysfunction and congestive heart failure (CHF), acute vascular events such as myocardial infarction and angina, and bleeding abnormalities.

Signaling through the VEGF pathway leads to several important vascular outcomes: increased capillary permeability, relaxation of vascular

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