Gynecologic Oncology xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Gynecologic Oncology

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

Review Article

# Assessment and management of diarrhea following VEGF receptor TKI treatment in patients with ovarian cancer

Joyce Liu [a], Shibani Nicum [b], Peter Reichardt [c], Kenneth Croitoru [d], Beate Illek [e], Manuela Schmidinger [f], Catherine Rogers [g], Christin Whalen [a], Gordon C. Jayson [g,*]

[a] Dana-Farber Cancer Institute, Boston, MA, USA
[b] Department of Oncology, University of Oxford, Oxford, UK
[c] Sarkomzentrum Berlin-Brandenburg, HELIOS Klinikum Berlin-Buch, Berlin, Germany
[d] Zane Cohen Centre for Digestive Diseases, Division of Gastroenterology, Mount Sinai Hospital, University of Toronto, Toronto, Canada
[e] Children's Hospital Oakland Research Institute, Oakland, CA, USA
[f] Department of Medicine I, Clinical Division of Oncology, Medical University of Vienna, Vienna, Austria
[g] Christie Hospital and Institute of Cancer Studies, University of Manchester, Manchester, UK

## HIGHLIGHTS

- VEGFR-TKIs are active agents in the treatment of ovarian cancer.
- VEGFR-TKI diarrhea can limit use of VEGFR-TKIs and requires careful management.
- VEGFR-TKI diarrhea should be assessed carefully.
- Life threatening causes of diarrhea must be excluded.
- VEGFR-TKI diarrhea should be treated with or without changes in dose schedule.

## ARTICLE INFO

*Article history:*
Received 8 January 2018
Received in revised form 20 March 2018
Accepted 23 March 2018
Available online xxxx

*Keywords:*
Ovarian cancer
Diarrhea
VEGF receptor tyrosine kinase inhibitor
VEGF
VEGFR
TKI

## ABSTRACT

Angiogenesis is a proven clinical target for the treatment of advanced epithelial ovarian cancer. Vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR-TKIs) offer patients potential new treatment regimens as they can be given as monotherapy, in combination with poly(ADP-ribose) polymerase (PARP) inhibitors, or with and following cytotoxic chemotherapy.

If VEGFR-TKIs are licensed for use in ovarian cancer, patients will require prompt and effective management of adverse events, including diarrhea, to optimize compliance and benefit. As diarrhea is one of the most prevalent toxicities of this class of drug, it is important to consider the potential causes, be they disease related (bowel obstruction), treatment related (VEGFR-TKI-related or infective/neutropenic septic diarrhea when patients are receiving cytotoxic chemotherapy combined with VEGFR inhibitor treatment), or incurred through diet.

Here, we provide an overview of the possible mechanisms responsible for VEGFR-TKI-induced diarrhea. We review potential interventions that can help in the management of diarrhea induced by VEGFR-TKIs, when used in combination or as single agents, and we provide a diarrhea treatment algorithm to serve as a clinical reference point for the management of diarrhea in patients with ovarian cancer treated with a VEGFR-TKI in combination with chemotherapy or PARP inhibitors, or as monotherapy.



**Contents**



* Corresponding author at: Christie Hospital and Institute of Cancer Studies, University of Manchester, 550 Wilmslow Road, Manchester, M20 4BX, UK.
*E-mail addresses:* snicum@nhs.net, (S. Nicum), peter.reichardt@helios-kliniken.de, (P. Reichardt), Ken.Croitoru@sinaihealthsystem.ca, (K. Croitoru), billek@chori.org, (B. Illek), manuela.schmidinger@meduniwien.ac.at, (M. Schmidinger), catherine.rogers@christie.nhs.uk, (C. Rogers), christin_whalen@dfci.harvard.edu, (C. Whalen), gordon.jayson2@christie.nhs.uk. (G.C. Jayson).

https://doi.org/10.1016/j.ygyno.2018.03.058
0090-8258/

Please cite this article as: J. Liu, et al., Assessment and management of diarrhea following VEGF receptor TKI treatment in patients with ovarian cancer, Gynecol Oncol (2018), https://doi.org/10.1016/j.ygyno.2018.03.058

## 1. Introduction

Ovarian cancer occurs in 239,000 women annually worldwide and is the leading cause of gynecologic cancer deaths in the UK and USA [1]. Angiogenesis, the formation of new blood vessels from pre-existing vessels, is a validated target for treating several tumor types through the use of inhibitors of the vascular endothelial growth factor (VEGF) pathway [2]. In ovarian cancer, angiogenesis is a proven clinical target, as demonstrated in Phase III trials of the humanized anti-VEGF antibody bevacizumab [3]. In addition to bevacizumab, inhibitors of angiogenesis include VEGF receptor tyrosine kinase inhibitors (VEGFR-TKIs) such as cediranib, pazopanib and nintedanib (Supplementary Table 1). These VEGFR-TKIs have the potential to offer additional therapeutic options for patients with ovarian cancer.

In ovarian cancer, recent studies have shown that when inhibitors of angiogenesis are combined with cytotoxic chemotherapy followed by maintenance monotherapy, response rate and progression-free survival (PFS) significantly improved, thus delaying the need for further cytotoxic chemotherapy [3–5]. Interestingly, when combined with the poly(ADP-ribose) polymerase (PARP) inhibitor olaparib, the VEGFR-TKI cediranib significantly improved PFS compared with PARP inhibitor treatment alone [6].

A known side effect of chemotherapy, VEGFR-TKIs (as monotherapy and in combination) and PARP inhibitors is an increase in the severity and incidence of diarrhea [6–9]. Diarrhea can be a debilitating and potentially life-threatening toxicity (Fig. 1, inset table) that can adversely affect a patient's health-related quality of life (HRQoL). Loss of fluids and electrolytes associated with persistent or severe diarrhea can result in life-threatening dehydration, renal insufficiency and electrolyte imbalances and may contribute to cardiovascular morbidity. Furthermore, reduced compliance because of adverse events (AEs) such as diarrhea may compromise clinical outcomes [10]. In the ICON6 trial of cediranib in combination with chemotherapy followed by cediranib maintenance treatment, AEs, particularly diarrhea, fatigue and hypertension, were problematic in some patients, and up to 39% of patients in the intervention arm, compared with 12% in the reference group, stopped the trial early because of toxic side effects [11].

VEGFR-TKIs are widely used in other cancers, including gastrointestinal stromal tumors (GIST) and renal cell carcinoma (RCC) [12,13]. Experience gained from the effective management of VEGFR-TKI-induced diarrhea in these tumor types may help to provide guidance for the successful management of diarrhea experienced by patients with VEGFR-TKI-treated ovarian cancer. Here, we provide an overview of the possible mechanisms responsible for VEGFR-TKI-induced diarrhea and the effects that such agents have had on patients who have participated in clinical trials. We also review potential interventions that can help in the management of VEGFR-TKI-induced diarrhea, when used either in combination or as single agents.

## 2. Mechanisms of VEGFR-TKI-induced diarrhea are unknown

The incidence of chemotherapy-induced diarrhea (CID) has been reported to be as high as 50–80% of patients (≥30% Common Terminology Criteria for Adverse Events [CTCAE] grades 3–5) [7], with most chemotherapeutic agents inducing diarrhea [14]. Similarly, VEGFR-TKI-induced diarrhea has been reported to be a common AE (Supplementary Table 1).

Understanding the pathophysiological mechanisms of diarrhea following anticancer therapies would lead to the development of effective treatments. The mechanisms for CID are becoming clearer and include severe intestinal damage caused by mucositis, carbohydrate or fat malabsorption, and/or indirect biological signaling, all of which have been outlined and discussed in detail previously [15–17]. Other potential causes of CID include overuse of antibiotics, underuse of antidiarrheal agents, malabsorption syndromes, concurrent radiotherapy and infection [18]. The involvement of intestinal chloride secretion has been recently considered as a mechanistic hypothesis [17]. However, the gastrointestinal tract has complex secretory, absorptive and propulsive functions that involve multifaceted neurologic, hormonal, muscular, immune and enzyme systems, along with multiple specialized cell types, which make it a difficult organ system to study. Mechanisms by which VEGFR-TKI-induced diarrhea occur are yet to be elucidated and may be distinct or overlap with those for CID.

In contrast to bevacizumab, which inhibits angiogenesis by binding to VEGF-A, multikinase inhibitors may affect more than VEGF-A signaling, and diarrhea is a more frequently observed side effect with this class of drugs. For example, VEGFR-TKI-induced diarrhea could be caused by inhibition of the receptor tyrosine kinases associated with VEGF-B or -C (VEGFR-1, -2 or -3) or by off-target inhibition of receptor tyrosine kinases, such as platelet-derived growth factor (PDGF), c-KIT, FLT3, etc. [8]. Other proposed mechanisms that could cause diarrhea relate to the widespread expression of VEGFRs in the intestine [19]. Indeed, the addition of VEGFR inhibitors significantly reduces the capillary network in pancreatic islets and intestinal villi, decreasing zymogen granules in the pancreas and pancreatic islet capillaries [8]. Consequently, patients treated with strong VEGFR inhibitors report watery, fatty stools (grade 3; >7 stools/day) [20].

VEGFR inhibitors may also cause changes to the bowel mucosa, leading to diarrhea. In the intestinal mucosa, small perturbations of blood flow can result in metabolic changes that resemble ischemia and hypoxia, which may cause diarrhea and ischemic colitis [21]. Inhibition of c-KIT by VEGFR inhibitors may result in altered bowel function by changing the regulation of interstitial cells of Cajal, the pacemaker cells of the intestine, potentially leading to bacterial overgrowth and diarrhea [22]. Together, these data suggest that a mixture of pancreatic, neurologic and vascular bowel function with potential bacterial overgrowth may account for VEGFR-TKI-associated diarrhea. However, the increased prevalence of diarrhea in patients receiving this class of drug compared with bevacizumab suggests that the mechanism is not solely related to VEGF-A, and further research is required.

## 3. Impact of diarrhea – clinical trial experience of diarrhea in ovarian cancer patients treated with VEGFR-TKIs

There are currently three VEGFR-TKIs, cediranib, nintedanib and pazopanib, which have been evaluated for the treatment of ovarian cancer in different disease settings. Supplementary Table 1 details the key

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