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WORD COUNT 2449
TIME SUBMITTED 27-MAY-2022 10:22PM
PAPER ID 86580561

Name of Journal: *World Journal of Gastrointestinal Endoscopy*

Manuscript NO: 76060

Manuscript Type: ORIGINAL ARTICLE

Retrospective Study

Safety of Endoscopy in Patients Undergoing Treatments with Antiangiogenic Agents: A 5-year Retrospective Review

Safety of endoscopy with antiangiogenic agents

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Abstract

BACKGROUND

Antiangiogenic agents (AAs) are increasingly used for treatment of malignant tumors and have been associated with gastrointestinal (GI) bleeding and perforation. Elective surgeries and endoscopy are recommended to be delayed for 31 days until after AAs treatment. Data regarding the safety of endoscopy while on antiangiogenic agents is extremely limited. No guidelines are in place to address the concern on holding these anti-angiogenic drugs.

AIM

To evaluate the risks of endoscopy in patients on antiangiogenic agents from 2015 to 2020 at our institution.

METHODS

This is a single centered retrospective study approved by the IRB of the institution. Patients that underwent endoscopy within 28 days of antiangiogenic agents' treatment were included in the study. Primary outcome of interest was death, and secondary outcomes included perforation and GI bleeding. Data were analyzed utilizing descriptive statistics. Fifty-nine patients were included in the final analysis and a total of eighty-five procedures were performed that were characterized as low risk and high risk.

RESULTS

Among the 59 patients a total of 85 endoscopic procedures were performed with 24 (28.2%) categorized as high-risk and 61 procedures (71.8%) as low-risk. Thirty patients (50%) were on bevacizumab whereas other patients were on imatinib (11.7%), lenvatinib (6.7%), ramucirumab (5%). The average duration between administration of AAs and the performance of endoscopic procedures was 9.9 days.

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performance of an elective endoscopic procedure, this should not delay the performance of an emergent or urgent endoscopic procedure given its good safety profile. Our study reiterates the safety data of low-risk endoscopic procedures in this sub-group of patients. This also generates further inquiry on whether there is a need to hold anti-angiogenics in patients on anti-angiogenics prior to high-risk endoscopic procedures. Awareness of newer medication and its implication on our current practice of gastroenterology are crucial for delivering optimal patient care. Future prospective studies should be evaluated in a multicentric larger population groups keeping in mind that the GI cancers have an inherent increased risk of bleeding & perforation.

MATERIALS AND METHODS

There is limited data on the safety of endoscopy in patients undergoing treatment with AA for oncological malignancies. Most recently, in a retrospective multi-center study by Kachaamy *et al*[7], the safety of endoscopy was investigated to identify adverse events and mortality in cancer patients being treated with AAs and undergoing endoscopy within 31 days of administration of AAs. It was concluded that endoscopy is well tolerated in patients on AAs and the incidence of adverse events was 0.7%, while the 30-day mortality was estimated at 6.5[7]. In our study, no procedural adverse events were observed, and the mortality rate was 2.35%. One of the two patient succumbed to persistent variceal bleeding, and the other patient died after transition to comfort care.

The first AA to be approved for use was bevacizumab for treatment of breast cancer and since then, AAs have played an integral role in the treatment of many oncological conditions[9]. Various AAs have shown a survival benefit for patients undergoing treatment of colorectal, liver, renal-cell, ovarian, endometrial, cervical, breast, and gliomas[10-14]. Bevacizumab and other AAs have been associated with poor wound-healing and increases the risk of complications if undergoing surgical and endoscopic procedures. Current literature suggest that the use of bevacizumab and other VEGF inhibitors can impair wound healing and potentially lead to severe wound healing

complications[3]. It is therefore recommended to delay elective surgeries for at least 28 days from the time of AA administration[15,16]. At present, there is no recommendation regarding the timing of endoscopic procedures among patients on AAs. Our study indicates that there were no procedure related AEs when AAs were administered within 28 days of an endoscopic procedure including high-risk ones.

Use of AAs have also been associated with an increased bleeding risk. This was demonstrated in a meta-analysis of 38 randomized controlled trials (RCTs) evaluating safety and efficacy of bevacizumab, which revealed a dose-dependent increased risk of bleeding (RR: 1.36 *vs* 2.87)[17]. Another meta-analysis evaluating 22 studies identified an incidence of high-risk bleeding of 2.8% (CI 2.1-3.8%) among patients receiving bevacizumab[18]. In comparison to the findings of the previously mentioned meta-analysis, our study did not identify any patients with post-procedure bleeding. However, one patient had persistent variceal hemorrhage despite attempts for endoscopic control with variceal ligation.

AAs have also been linked with increased gastrointestinal perforation especially if endoscopic interventions like colonic self-expanding stents (SEMS) are attempted. The rate of perforation ranges between 2-12% among patients undergoing SEMS placement[19,20]. A meta-analyses evaluating effectiveness and safety of monoclonal antibodies including bevacizumab, cetuximab and panitumumab it was concluded that the use of these agents have serious adverse events including gastrointestinal perforation[20]. This risk of gastrointestinal perforation even with the performance of high-risk endoscopic procedures was not seen in our study which supports the findings of the multicenter outcome study by Kachaamy *et al*[7] regarding the safety of endoscopy among patients on AAs.

Strengths of our study include the removal of any potential selection bias with the inclusion of all patients who underwent endoscopic procedures while on AAs. Given that our facility is not an NCI-designated cancer center, the findings of our study are generalizable and applicable to the general practice. Nonetheless, this study is limited by its retrospective nature and small sample size.

RESULTS

Patient Characteristics

Fifty-nine patients (M/F = 25/34) were included in this study who underwent a total of 85 endoscopic procedures. The mean age of the study population was 64.9 years at the time of endoscopy. Majority of the patients were Caucasians (54.2%) or African Americans (40.7%). The most common malignancy types were colorectal cancer (20.7%), liver (11.9%), ovarian (10.2%) and lung (10.2%); and the majority (59.3%) had stage IV metastatic disease at the time of endoscopy (refer to Table 1). Thirty patients (50%) were on bevacizumab whereas other patients were on imatinib (11.7%), lenvatinib (6.7%), ramucirumab (5%) as detailed on table 2. One of the patients with the diagnosis of acute myeloid leukemia (AML) who was being treated with two anti-angiogenic agents bevacizumab and sorafenib.

Procedures

A total of 85 endoscopic procedures were performed with 24 (28.2%) categorized as high-risk and 61 procedures (71.8%) as low-risk. High risk procedures included variceal bleeding control, percutaneous gastrostomy tube placement, pneumatic balloon dilation, and stent placement while low-risk included diagnostic procedures along with mucosal biopsies. The average duration between administration of AAs and the performance of endoscopic procedures was 9.9 days.

Adverse Events and Mortality

Among the eighty-five endoscopic procedures that were performed, there were no procedure related adverse events that were documented. One patient on lenvatinib therapy for metastatic hepatocellular carcinoma had persistent bleeding despite esophageal variceal banding and died 4 days later from hemorrhagic shock. Another patient on sorafenib therapy for AML died 24 days after an EGD with biopsy while on hospice care.

DISCUSSION

Study Design and Patient Population

This is a single center retrospective study conducted at a non-National Cancer Institute (NCI) designated hospital specializing in treatment of cancers in the state of Georgia, USA. Inclusion criteria for the study were: 1) patients receiving treatment with AAs including vascular endothelial growth factor (VEGF), vascular endothelial growth factor receptor (VEGFR) inhibitors, epidermal growth factor receptor (EGFR) inhibitors, multi-targeted tyrosine kinase inhibitors, and mammalian target of rapamycin (mTOR) inhibitor, 2) patients undergoing endoscopic procedures within 28 days of AA administration between from January 1, 2015 – March 31, 2020. Exclusion criteria included: 1) age less than 18 years old. All patients undergoing endoscopic procedures within 28 days after administration of AAs were included in the study analysis. The Augusta University Investigation Review Boards approved this study.

Patients who met the inclusion and exclusion criteria were identified using I2B2 software, and details regarding the endoscopic procedures and the timing of AA administration were obtained from the electronic medical records. Endoscopic procedures were categorized as either high risk or low risk based on existing literature regarding endoscopic procedural risks associated with antithrombotic agents[8]. Low risk procedures included diagnostic endoscopies or with biopsy. In contrast, high risk procedures consisted of stent placements, gastrostomy tube placements, snare polypectomy, endoscopic retrograde cholangiopancreatography (ERCP), and endoscopic ultrasound (EUS) with fine needle aspiration (FNA).

Statistical Analysis

Statistical analyses were performed utilizing simple descriptive statistics including percentages and frequencies. The demographic data, the mortality rate and the endoscopic adverse events were analyzed using descriptive statistics. The primary outcome measure was mortality rate within 30 days of endoscopy whereas the secondary outcome measures were procedure-related adverse events such as bleeding

and perforation within 30 days of endoscopy. The adverse events were labeled according to the common terminology criteria for adverse events (CTCAE) version (have version 5.0 now) which defines adverse events (AEs)as an unintended and unfavorable outcome associated with a medical treatment or procedure that may or may not be associated to the medical treatment or procedure. Classification of the severity of AEs were based on a grading system from 1 to 5 wherein 1 is mild, 2 is moderate, 3 is severe, 4 is life-threatening and 5 is death. The mortality rate and incident rate of AEs were determined using the total number of study participants as the denominator.

CONCLUSION

Angiogenesis is a complex process of forming vascular network by endothelial cells proliferation mediated by growth factors like vascular endothelial growth factors (VEGF), insulin like growth factors (IGF), fibroblast growth factors (FGF) and hypoxia inducible factors (HIF-1). It is first initiated during embryogenesis from mesodermal precursor cells, later repeated during process of healing. Similarly, when tumor cells are subjected to hypoxia, they produce growth factor leading to angiogenesis. This not only provide a source of nutrition but also a means for metastasis.

Folkman postulated the idea of antiangiogenic agents (AAs) as an effective cancer therapy in early 1970[1]. Currently, AAs are widely used in the treatment of malignant tumors owing to their effectiveness in increasing survival. Monoclonal antibodies, VEGF decoy receptor, and small molecule tyrosine kinase inhibitors are three major classes of anti-angiogenics currently in clinical practice[2]. However, VEGF also play a crucial role in wound healing and the use of AAs may potentially lead to complications such as bleeding and impaired wound healing[1,3].

Post-procedure adverse events were higher among patients receiving AAs[4]. The potential for increased occurrence of complications such as bleeding among cancer patients on AAs after procedures have led to the postponement of elective surgical procedures and endoscopies for at least 28 days after AA treatment. The mechanism of

gastrointestinal (GI) perforation is attributed to splanchnic or mesenteric thrombi, impaired healing & proliferation, decreased blood supply to intestinal wall, and decreased stability secondary to tumor destruction have been postulated[5]. There is limited and inconsistent data in the literature regarding the rate of adverse events during endoscopy among patients on AAs. Imbulgoda *et al* reported two complications of perforation (2/80 patients) in patient receiving bevacizumab while undergoing placement of self-expanding metal stent[6]. More recently Kachaamy *et al*[7] revealed a low adverse event of 1.6% (7/455) in patients receiving AA. The cautious approach of delaying even low risk endoscopic procedures among patients receiving AAs may have resulted from the extrapolation of findings from studies of surgical procedures where increased adverse events like bleeding and impaired wound healing were observed[4]. It is important to note that endoscopic procedures are not as invasive as other surgical procedures and recommendations should not be solely based on data from surgical procedures.

In this single centered study, we reviewed medical records of the patients who underwent GI endoscopy after receiving anti-angiogenics therapy within the past 28 days. Here we aim to investigate 30-days adverse events in patients receiving AA undergoing an endoscopic procedure.

ARTICLE HIGHLIGHTS

Research background

High-grade bleeding and perforation are some of the associated side effects of antiangiogenic agents. The safety of endoscopy in patients receiving this therapy is unknown. Here we attempt to explore the incidence of bleeding, perforation, and mortality in our single centered study.

Research motivation

With the increased survival of cancer patients with newer chemotherapy, more patients would require endoscopic procedures for further surveillance and screening. It is

important to assess the safety of endoscopic procedures among patients receiving therapy such as antiangiogenic agents who are at higher risk for bleeding and perforation.

Research objectives

Our objective is to understand the risk of endoscopy in patients on antiangiogenic agents.

Research methods

We performed a retrospective analysis of patients admitted to the hospital on antiangiogenic agents to our institute. We used simple descriptive statistics to assess primarily mortality within 30 days of the procedure along with the incidence of bleeding and perforation.

Research results

We found no procedure-related adverse events in our small population study among the patients receiving antiangiogenic agents. These results need to be further confirmed in a multicentric larger population group.

Research conclusions

Our study reveals that endoscopic procedures are safe in patients receiving antiangiogenic agents. It affirms to not delay emergent or urgent endoscopic procedures among this population.

Research perspectives

Future research should be carried out in a multicentric, larger group of the population to further assess the safety of the endoscopic procedure among this population group.

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