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CASE REPORT

Pazopanib Monotherapy Is Active in Relapsed and Refractory Metastatic Gastroesophageal Adenocarcinoma and Can Produce Durable Response

Vineet Govinda Gupta[1] · Ranga Rao Rangaraju[1] · Rajat Saha[2] · Peush Bajpai[1]

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Background

Metastatic gastroesophageal adenocarcinomas (GEA) constitute a challenging treatment problem. Two-thirds of all patients will either present with or develop metastatic disease over the course of their therapy. Despite advances in treatment, the prognosis of metastatic GEA remains poor with a median survival of less than 1 year, except perhaps for HER2/*neu*-amplified patients who can achieve better outcomes with the integration of HER2-directed targeted therapy [1]. The standard systemic therapy for metastatic GEA comprises palliative-intent chemotherapy, with multiple active agents given in several sequential "lines" of therapy. The most active agents tend to be platinum agents, fluoropyrimidines, and taxanes. However, fitness for chemotherapy, response rates, and progression-free survival drops from one line to the next due to disease progression and side effects of previous treatment.

Angiogenesis plays an important role in gastric cancer growth and spread, and high vascular endothelial growth factor (VEGF) expression is associated with tumor aggressiveness. Expression of VEGF in resected gastric cancer is associated with more poorly differentiated cancers, higher stage, greater lymphatic and vascular involvement, higher nodal and liver involvement, and poorer prognosis [2, 3]. This realization has led to various trials of antiangiogenic agents in setting of advanced GEA. Bevacizumab failed to secure approval for the treatment of advanced GEA as two large randomized controlled trials failed to reach their primary end points [4, 5]. However, the VEGF-A antagonist ramucirumab was approved based on a survival benefit seen in two randomized controlled trials, REGARD and RAINBOW [6, 7]. However, the use of ramucirumab is limited by its need for intravenous administration and significant cost, which some have commented to be non cost-effective [8].

The use of oral tyrosine kinase inhibitors (TKIs) may be another approach to inhibition of angiogenesis in advanced GEA. Oral agents are generally better tolerated and acceptable to patients as compared to intravenous agents, which require venous access and more frequent clinic visits. Several agents have been tried in this setting, including apatinib, sunitinib, sorafenib, pazopanib, and regorafenib [9]. Pazopanib is an oral multi-targeted tyrosine kinase inhibitor (TKI) which inhibits vascular endothelial growth factor receptors (VEGFR) 1, 2, and 3, platelet-derived growth factor receptors α and β, and stem cell factor receptor (c-kit) [10]. The toxicity profile of pazopanib is generally well manageable and has even been demonstrated to be superior to sunitinib with similar efficacy in another cancer subtype [11]. Thus, oral pazopanib may be a good option for patients after failure or intolerance to frontline therapies. The agent has been studied previously in GEA, albeit in the frontline setting and in combination with chemotherapy. Here, we present our experience with this agent as monotherapy in four cases of metastatic GEA who had exhausted standard lines of therapy.

Cases

Case I

An 81-year-old lady presented with abdominal discomfort and on evaluation was diagnosed with moderately differentiated adenocarcinoma of the stomach. She initially underwent an upfront subtotal gastrectomy which revealed pT2N1M0 disease. Following surgery, the MDT recommended adjuvant chemotherapy. After two cycles of reduced dose capecitabine

✉ Vineet Govinda Gupta
vineetgovindagupta@gmail.com

[1] Department of Medical Oncology, Max Super Speciality Hospital, B-2 Basement, Shalimar Bagh, New Delhi, India

[2] Department of Medical Oncology, Max Super Speciality Hospital, Patparganj, New Delhi, India

and oxaliplatin, chemotherapy had to be discontinued due to intolerance. Thereafter, she was kept on surveillance with 6 monthly endoscopy and CT imaging. After 10 months, she complained of intermittent abdominal pain. A PET-CT scan revealed multiple enlarged FDG-avid lymph nodes in the periportal and portocaval locations, suggesting relapse. She received six cycles of nab-paclitaxel, which led to a partial remission. However, this was at the cost of grade 3 peripheral neuropathy. At this point, the MDT concluded that it was unlikely that she would be fit for any subsequent chemotherapy at the next inevitable relapse, and recommended maintenance therapy with a low toxicity agent to prolong progression-free survival, if possible. An attempt was made to use S1 at low dose as a single agent but was not tolerated. As she was not considered a candidate for more chemotherapy and ramucirumab was unavailable at that time, she was started on oral pazopanib 400 mg twice daily on an empty stomach. The chief toxicity faced by her was a yellowish skin discoloration and intermittent diarrhea, but dose reduction was not required. A PET-CT scan done after 6 months revealed a radiological complete remission, which was durable on subsequent scans. At present, she is alive and disease-free more than 5 years from initial recurrence, and is on continuous pazopanib with an excellent quality of life.

Case II

A 38-year-old female presented with abdominal pain. Imaging was suggestive of thickening of distal gastric wall predominantly involving the gastric antrum, with a bulky left ovary with no other site of disease. Endoscopic biopsy revealed a poorly differentiated adenocarcinoma. The initial surgery consisted of a radical distal gastrectomy with a D2 lymphadenectomy and left oophorectomy. Histology was suggestive of pT2N1M1 disease including histologically proven left ovarian infiltration with poorly differentiated adenocarcinoma. Following surgery, imaging revealed a bulky right ovary. She then underwent multiple sequential lines of therapy, namely docetaxel, oxaliplatin and 5-fluorouracil, irinotecan-cisplatin, and epirubicin-capecitabine. In view of persistent disease in right ovary, a right oophorectomy was performed (histology revealed adenocarcinoma infiltration) and she was rendered radiologically disease-free. In view of metastatic disease, an MDT discussion was done and it was recommended to add maintenance therapy to extend progression-free survival. Ramucirumab was unavailable in the country at that time and she was placed on oral pazopanib 400 mg twice daily. Pazopanib was well tolerated, sequential radiology revealed no evidence of relapse. At present, the patient has been on pazopanib for two and a half years and is alive and radiologically disease-free.

Case III

A 41-year-old male presented with initially localized disease siewert type-1 lower esophageal adenocarcinoma. He was treated with upfront surgical resection which revealed pT3N3M0 disease. In view of high-risk disease, the MDT recommended adjuvant radiation as well as chemotherapy. He received chemotherapy with capecitabine and oxaliplatin followed by local radiation. The end of therapy PET-CT showed a complete remission. Unfortunately, he developed a local recurrence 15 months after initial treatment. A resection was done which was followed by concurrent chemoradiation with capecitabine, docetaxel, and intensity-modulated radiotherapy, which rendered him disease-free. He suffered a second recurrence at the surgical margins and mediastinal lymph nodes 10 months later. Thereafter, he received palliative systemic therapy with docetaxel, oxaliplatin, and 5-fluorouracil. After an initial response, he progressed and received irinotecan with capecitabine. At next progression, he was considered for ramucirumab but it was not preferred due to poor affordability. Therefore, he was given pazopanib orally at 400 mg twice daily which was well tolerated. However, he progressed 4 months later. He failed to respond to subsequent therapies and passed away 7 months from starting pazopanib.

Case IV

A 57-year-old male presented with chest pain and was subsequently diagnosed to have metastatic gastric adenocarcinoma with lung and bone metastases. He received palliative radiotherapy to bone metastases which was followed by sequential lines of palliative chemotherapy, initially docetaxel, oxaliplatin and 5-fluorouracil, and then irinotecan with carboplatin. He responded to the latter, but developed disease progression after six cycles. Ramucirumab was not offered due to limited affordability. He underwent a palliative gastric tumor wedge resection, and thereafter was started on pazopanib 400 mg twice daily. He did not report any side effects nor any dose modifications done for him. However, 3 months after treatment initiation, he was noted to have progressive disease on radiology and pazopanib was stopped. He received four further lines of therapy post-pazopanib, and ultimately passed away 16 months from starting pazopanib (26 months from initial diagnosis).

Discussion

Inhibition of angiogenesis is an established approach to treatment of advanced GEA in the relapsed setting. The drug ramucirumab is FDA-approved both as a single agent and in combination based on survival benefit seen in phase III trials [6, 7]. However, this drug suffers from important limitations

of cost and availability, and is often considered to be cost-ineffective for the small benefit it provides. Additionally, it is an intravenous agent, which is often not preferred by patients in the refractory setting as it mandates more frequent hospital visits and increased costs.

The orally active antiangiogenic TKIs represent an attractive alternative in this setting. Pazopanib is our agent of choice by extrapolation of data from renal cancer because it has shown relatively low toxicity with similar efficacy as sunitinib, making it a first-line option in this cancer [11]. Only one previous trial has studied pazopanib specifically in metastatic GEA. This study was performed in the frontline setting among advanced gastric cancer patients. Pazopanib was offered in combination with capecitabine and oxaliplatin, leading to a 92.4% disease control rate (DCR), a 62.4% overall response rate (ORR), and a median progression-free survival (PFS) and overall survival (OS) of 6.5 and 10.5 months respectively [12]. In another study, pazopanib was added to a regimen of paclitaxel and carboplatin in a variety of solid tumors having received varying prior therapy. Only two patients with gastro-esophageal cancer were included, and one of them achieved a partial response [13].

However, there is no reason to believe that using chemotherapy with pazopanib as combination would be the optimum approach to the incorporation of this agent. Combinations of antiangiogenic TKIs with chemotherapy have often failed to demonstrate benefits over single modality in other cancers [14]. Also, combination therapy is anticipated to increase toxicity and reduce tolerability [15], which in turn can lead to treatment interruptions and dose reductions which would worsen disease-related outcomes. In fact, the ability of patients to receive full doses was an issue with both trials discussed above. In one of the trials [12], the dose of capecitabine was lower than the standard regimen, and in the other, full dosing (800 mg daily) of pazopanib was not possible since three out of four patients in that cohort developed dose-limiting toxicity [13]. Since we wanted a tolerable regimen with good patient compliance in the second-line (or later) setting, we preferred to use pazopanib as a single agent and not as combination.

Among the four cases described above, two patients failed to respond to pazopanib (and showed progressive disease at the first follow-up assessment). However, two other patients demonstrated remarkable responses, achieving complete remissions which were durable despite having metastatic disease. While this case series is too small to make any definitive conclusions, both patients had minimal disease burden before starting pazopanib, case I having underwent chemotherapy leading to a partial response, and case II having undergone surgery to render him macroscopically disease-free prior to starting pazopanib. One hypothesis that may be drawn is that pazopanib is effective in controlling minimal residual disease but its impact on progressive macroscopic disease is more limited. In fact, the positive data with regard to pazopanib in ovarian cancer is noted in the maintenance setting, after disease burden has been reduced with chemotherapy [16]. Similar conclusions with reference to maintenance approach have also been applied to the use of bevacizumab in various cancers [17–19]. It may be argued that case 2 was surgically disease-free when pazopanib was started; however, Krukenberg metastases generally carry an extremely poor prognosis and these patients are usually not considered curable [20].

Another hypothesis regarding the good response seen in two patients may have to do with a "sensitive" disease biology. Studies in gastric cancer cell lines reveal that fibroblast growth factor receptor 2 (FGFR2) amplification may be a predictor of tumor sensitivity to pazopanib [21]. In the previously mentioned first-line prospective trial, 7/54 patients had FGFR2 expression by immunohistochemistry and the response rate was very high in this population (86% response rate, 14% stable disease, no progressors). We were unable to test our patients for FGFR2 expression or amplification, although it could be a reasonable explanation for the remarkable outcomes seen in case I and II.

To conclude, our experience with pazopanib as a single agent given in advanced GEA demonstrates that it has the potential to produce good outcomes in a subset of patients with low-burden disease. Differences in disease biology are expected to play an important role in pazopanib sensitivity. Despite the limitations of a case series, a number of characteristics of pazopanib make it an attractive agent as monotherapy in patients who have progressed on first-line therapy: Its activity has been demonstrated in preclinical studies; its toxicity is well-understood, generally low, and easily managed; and the drug is orally available and often cheaper than alternative therapies. Formal prospective studies may help better define the role of this drug in the treatment of metastatic GEA.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent For this type of study, formal consent is not required.

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