Temsirolimus therapy and small bowel perforation in a pediatric patient with Clostridium septicum bacteremia

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Abstract

Temsirolimus has been demonstrated to result in significant disease stabilization in children with high-grade glioma, neuroblastoma, and rhabdomyosarcoma. While mucositis has been reported as a common adverse effect of temsirolimus therapy in adult and pediatric patients, bowel perforation is an infrequent and life-threatening side effect of temsirolimus in adults and has not previously been reported in children. We present a case treated with temsirolimus for recurrent metastatic rhabdomyosarcoma who underwent ileocecectomy and small bowel resection for perforation with frank necrosis. His presentation was complicated by Clostridium septicum infection, a rare, frequently fatal, gastrointestinal pathogen associated with malignancy and bowel ischemia.

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Temsirolimus is an ester of sirolimus (rapamycin) and a highly specific inhibitor of mammalian target of rapamycin (mTOR). Inhibition of mTOR reduces expression of vascular endothelial growth factor (VEGF) via inhibition of hypoxia-inducible factor alpha-1 (HIF-1α), an important pro-angiogenic factor. Temsirolimus has potent antitumor activity and is approved by the United States Food and Drug Administration (FDA) for the treatment of advanced renal cell carcinoma [1]. Several mTOR inhibitors, including temsirolimus, have demonstrated significant antitumor activity in both in vivo and in vitro pediatric solid tumor models, including rhabdomyosarcoma [2,3]. A recent phase I/II study of temsirolimus monotherapy for relapsed high-grade glioma, neuroblastoma, or rhabdomyosarcoma resulted in disease stabilization [4].

Mucositis has been reported as a common adverse effect of temsirolimus therapy in both adult [5–8] and pediatric patients [4,9,10]. In the report summarizing the FDA’s approval of the drug for treatment of advanced renal cell carcinoma (RCC), mucositis occurred more commonly in patients receiving temsirolimus (41%) than in those receiving interferon-alpha (IFN-α) (10%) [5]. Bagatell et al. reported one pediatric patient with grade 3 oral mucositis; however, the majority of pediatric cases were low-grade (Grade 2; n = 11, observed in cycles 1 and 2) and tended to improve during subsequent cycles of therapy [9].

Bowel perforation has been described as an infrequent and life-threatening side effect of temsirolimus in adults [5,6]. Two cases of perforation were diagnosed in the phase III trial of temsirolimus for renal cell carcinoma, one in the temsirolimus arm and one in the combination (temsirolimus plus IFN-α) arm. An additional seven cases, including four fatalities, were identified in the temsirolimus safety database [5]. Bowel perforation was associated in one autopsy study with Grade IV mucositis in the affected patient and the continued use of temsirolimus was cautioned in patients who experienced severe mucositis. To date, no reports of bowel perforation associated with temsirolimus use in the pediatric patient population have been published in the indexed literature.

1. Case description

A 17-year-old male undergoing treatment for relapsed testicular embryonal rhabdomyosarcoma with temsirolimus, vincristine, and cyclophosphamide (ARST0921) presented with acute onset of
severe abdominal pain, fever, nausea, and non-bloody, non-bilious emesis. His past oncologic history was characterized by a radical inguinal orchiectomy for the removal of a large left testicular mass 4 years previously. Pathology revealed embryonal rhabdomyosarcoma, spindle cell variant, with evidence of lymphovascular invasion. Additional staging via bilateral bone marrow biopsies, left inguinal node biopsy, chest CT scan, and bone scan were negative and he was characterized as stage II, group II. He

![Fig. 1. Computed tomography with intravenous contrast of the patient upon presentation (A: ascites; B: extraluminal free air; C/D: bowel wall thickening and pneumatosis.).](image1)

![Fig. 2. Surgical pathology (A: Segment of ileum showing focal ulceration; B: Site of ulceration with transmural gas filled cysts (H&E 20×); C: Congested bowel mucosa with pseudomembrane formation (arrow, H&E 40×); D: Site of ulcer with Gram positive spore forming bacilli, consistent with Clostridium Sp. [B&B 400×]).](image2)
received treatment per Children’s Oncology Group protocol ARST0331 with vincristine, actinomycin and cyclophosphamide as well as adjuvant radiotherapy with 36 Gy to the left lower pelvis and groin. Three years after completion of therapy he presented with a 12 cm left retroperitoneal mass and concurrent obstructive uropathy. Gross total resection was performed, pathology indicated recurrent tumor, and he initiated chemotherapy for relapsed disease. Due to severe stomatitis and pharyngitis during cycles 1 and 2, the patient’s temsirolimus dose was reduced and Day 15 temsirolimus was omitted over several cycles.

On day #14 of Cycle #11 of ARST0921 the patient presented to the Emergency Room with diffuse peritonitis. A computed tomography (CT) scan demonstrated ascites, free air, ileal inflammation and pneumatisoasis with perforation into the mesentery (Fig. 1). He was tachycardic and febrile to 40°C with a WBC Count of 15,100 cells/mcl, having recovered from a nadir of 1300 one week prior. Upon emergent exploratory laparotomy the patient was found to have full thickness necrosis of the terminal ileum just proximal to the ileocecal valve with perforation of this segment into the mesentery. Gross pneumatisositis was seen extending 10 cm proximal to this area of perforation. Additionally, a frankly ischemic segment of mid-ileum was identified with apparent thrombosis of the distal branches of mesenteric blood supply. Ileocecectomy and a separate resection of mid-ileum were performed.

Surgical pathology revealed small bowel with transmural ischemic necrosis, focal pseudomembrane formation, extensive intramural pneumatisositis, occasional organizing thrombi, focal myonecrosis of muscularis propria and serosa with fibrinopurulent exudate (Fig. 2). Stains for microorganisms showed the presence of Gram positive bacilli with rare terminal spores morphologically consistent with Clostridial species and blood clutures drawn prior to surgical intervention grew out Clostridium septicum.

2. Discussion

The mechanism by which temsirolimus causes bowel perforation has not been fully elucidated. mTOR inhibitors have been found to modulate cell proliferation, angiogenesis, and immune function by decreasing the expression of both HIF-1α and HIF-2α and inhibiting VEGF activity. Bevacizumab, a targeted VEGF inhibitor, has a well-described association with bowel perforation [11]. Speculated causes include disruption of the coagulation balance and secondary ischemic thrombosis by induction of Factor III, von Willebrand factor, and plasminogen activator [12]. Additionally, inhibition of cellular microcirculation may impair normal mucosal turnover and repair mechanisms. Because mTOR inhibitors also inhibit VEGF activity, these mechanisms may be extrapolated to temsirolimus [6].

Moreover, the unesterified parent molecule of temsirolimus, sirolimus, a drug used routinely for immunosuppression following solid organ transplant, is also frequently associated with gastrointestinal complications including oral lesions and small bowel and colon ulceration and perforation [13]. Sirolimus has been specifically implicated in small bowel perforation when used in combination with a calcineurin inhibitor [14,15]. Symptomatic ulceration of the small bowel has been reported in patients treated with sirolimus, with resolution following discontinuation of the drug [16]. It is important to note that this patient’s chemotherapy regimen included two agents in addition to temsirolimus (cyclophosphamide and vinorelbine) both of which have been associated with gastrointestinal complications in the setting of neutropenic [17]. Between the years 2004 and 2014, 4 cases of vinorelbine associated bowel perforation were reported, all in adults and all in combination with an angiogenesis inhibitor (bevacizumab, imatinib) [18,19]. A possible role for these agents contributing to the pathogenesis of small bowel perforation cannot completely be excluded.

Only 1000 to 3000 cases of C. septicum are reported in the United States annually, few of which occur in children [20]. A recent review found that the majority of C. septicum infections in children occur in the presence of coexistent perturbations in neutrophil function, as may occur in malignancy or congenital or cyclic neutropenia, or in the presence of bowel ischemia [20]. Typhilitis or necrotizing enterocolitis of the colon with extensive involvement of the cecum and ileocecal junction is common in cases of C. septicum infection which carries with it a 70–80% mortality [20,21]. It has been proposed that both malignancy and the immunosuppressant effects of chemotherapy can impair the immune function and integrity of the gastrointestinal mucosa to allow penetration and colonization by the species with subsequent bloodborne “metastatic” spread [21–23].

In conclusion, we present a 17-year-old male with a history of temsirolimus therapy for recurrent metastatic rhabdomyosarcoma who underwent an ileocecectomy and small bowel resection for small bowel perforation and necrosis, complicated by C. septicum infection. Several adult reports have linked temsirolimus-related bowel perforation with mucositis and have proposed that temsirolimus mediated VEGF inhibition may cause bowel ischemia. This ischemia and resulting ulceration/perforation may have provided a supportive environment for Clostridium septicum superinfection. Future investigations should further delineate the risk of bowel perforation and/or superinfection by necrotizing microorganisms associated with temsirolimus therapy for solid tumors in the pediatric population.

Conflict of interest
Nothing to declare.

References


