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CORRESPONDENCE

Long-term aprepitant for nausea and vomiting associated with gastroparesis in hematopoietic stem cell transplantation

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Nausea and vomiting in the course of allogeneic hematopoietic stem cell transplantation (SCT) is common and might persist up to months. Despite modern antiemetic guidelines, control of nausea in children sometimes is not possible [1]. A 3-day regimen of the antiemetic (fos)aprepitant, a neurokinin-1 receptor antagonist, has been licensed for the treatment of chemotherapy-induced nausea and vomiting (CINV) [2]. In this letter, we describe our experience with long-term off-label use of aprepitant to relieve late nausea and vomiting in the course of SCT.

A 15-month-old boy (patient A) with hemophagocytic lymphohistiocytosis was transplanted with bone marrow from a fully matched unrelated donor. Chemotherapeutic conditioning consisted of treosulfan, fludarabine, and alemtuzumab, with methotrexate and cyclosporine as graft versus host disease (GvHD) prophylaxis. Despite several antiemetic regimens (ondansetron, lorazepam, erythromycin, domperidone, alizapride) and a proton pump inhibitor, nausea and vomiting persisted after transplantation. Upper gastrointestinal endoscopy and sigmoidoscopy did not show GvHD or infection (cytomegalovirus, helicobacter pylori, candida). Eventually, he was diagnosed with gastroparesis. Placement of a duodenal feeding tube failed. Introduction of enteral feeding was repeatedly attempted but resulted in recurrence of abdominal pain and vomiting. Two months after transplantation he was discharged with parenteral feeding. After three months without clinical improvement, a trial of aprepitant was considered. After parental consent, aprepitant (1.5 mg/kg once daily, no loading dose) was started during clinical observation. Within 24 h after the start of aprepitant a clear improvement of symptoms was observed. Enteral nasogastric feeding was tolerated and daily aprepitant was continued for four months, without side effects or toxic drug interactions. After one and a half month of treatment with aprepitant, the dosing frequency was decreased for a short period from once daily to once every other day, however, vomiting increased. Eight months after transplantation, aprepitant was successfully discontinued. At this timepoint, the patient resumed oral food intake, and nine months after transplantation the enteral nasogastric feeding could be stopped.

A 5-month-old boy (patient B) was referred for SCT because of acute myeloid leukemia (AML). Extramedullary lesions and central nervous system involvement were present at diagnosis. Before referral, treatment consisted of mitoxantrone, etoposide, cytarabine and intrathecal methotrexate. Conditioning consisted of anti-thymocyte globulin, thiotepa, treosulfan, and fludarabine, with cyclosporine and prednisone as GvHD prophylaxis. The patient was transplanted with unrelated cord blood. Because of severe neutropenic enterocolitis he was on total parenteral nutrition and minimal enteral feeding. Emesis was controlled with granisetron, lorazepam, and fosaprepitant (2 mg/kg once daily, loading dose 3 mg/kg once) in addition to a proton pump inhibitor. Elevated liver enzymes were attributed to either drug-induced hepatotoxicity or total parenteral nutrition. Possible drugs attributing to hepatotoxicity were voriconazole and fosaprepitant. Voriconazole was switched to micafungin and fosaprepitant was temporarily ceased. These interventions were spaced one week apart. Liver enzymes subsequently returned to baseline. After 2 weeks, enteral aprepitant (2 mg/kg once daily, no loading dose) was started in addition to ondansetron because of increasing complaints of nausea and vomiting. He was eventually discharged with daily aprepitant, as several attempts to stop

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aprepitant were unsuccessful due to vomiting. No drug-induced liver toxicity or drug interactions were observed. Finally, after 3 months aprepitant could be stopped.

A 19-month-old girl (patient C) with myelodysplastic syndrome with refractory cytopenia was transplanted with bone marrow from a fully matched unrelated donor. Conditioning consisted of anti-thymocyte globulin, treosulfan and fludarabine, with methotrexate and cyclosporine as GvHD prophylaxis. During conditioning, ondansetron monotherapy was given with good effect. The day before SCT the antiemetic regimen was adapted to a combination of granisetron, chlorpromazine and fosaprepitant (2 mg/kg once daily for 3 weeks, loading dose 3 mg/kg once). Because of intolerance for enteral feeding, parenteral feeding was given for one and a half weeks and a proton pump inhibitor was started. In the fourth week after SCT, she was discharged with ondansetron and enteral feeding. However, 2 weeks after discharge, vomiting reappeared. Vomiting occurred predominantly after enteral feeding. Also, she had a new onset abdominal pain. Our working diagnosis was unexplained gastroparesis. As placement of a duodenal feeding tube was unsuccessful, aprepitant (2 mg/kg once daily, loading dose 3 mg/kg once) was started in the outpatient setting. Shortly after the start of aprepitant the parents reported that vomiting had ceased, whereas a mild abdominal pain persisted. Appetite came back and aprepitant was stopped after being used for 3 weeks without apparent adverse effects.

CINV belongs to the most bothersome side effects of chemotherapy, and children occasionally experience persistent nausea and vomiting up to several months after allogeneic hematopoietic SCT.

The chemotherapeutic conditioning regimen preceding SCT is the most common cause of nausea and vomiting in the first week following SCT. Briefly, chemotherapy acts on the chemotherapy trigger zone in the brain stem, activating the vomiting center, increasing efferent output in the target organs of the gastrointestinal tract, eventually resulting in emesis [3]. Using the validated pediatric nausea assessment tool, comprising of self-reported nausea and a visual analog scale, it has been shown that control of CINV, despite prophylaxis, is exceedingly poor in children receiving myeloablative chemotherapy for SCT conditioning [1, 4].

The differential diagnosis of delayed nausea and vomiting after SCT includes GvHD, enteric infections (cytomegalovirus, herpes viruses, helicobacter pylori, candida), gastroparesis, adverse effects of medication, anticipatory vomiting, stress, and idiopathic. Especially gastroparesis seems to be a common cause of nausea, vomiting, and bloating after SCT [5]. In the patients described above, we believe gastroparesis contributed to their symptoms. Although antiemetics have not been specifically tested in gastroparesis, they may relieve nausea and vomiting [6].

Aprepitant is a neurokinin-1 receptor antagonist and consequently is able to alleviate the emetic effects of the neurotransmitter substance P. Aprepitant has been licensed for the treatment of acute (0–24 h) and delayed (up to 120 h) CINV for age 6 months and older. Dosing is 3 mg/kg for the first day followed by 2 mg/kg for day 2 and 3. Longer use is unlicensed as sufficient data is lacking [2]. In patient B a possible significant adverse event was observed as (fos) aprepitant had to be stopped temporarily because of possible drug-induced toxic liver injury. (Fos)aprepitant is rarely associated with clinically apparent liver injury [7]. With hindsight, we believe the pattern of elevation of liver enzymes was more likely associated with voriconazole treatment and not with (fos)aprepitant administration. Aprepitant could also be restarted later in the SCT course without apparent elevation of liver enzymes. Our observations suggest that aprepitant is generally well tolerated. Aprepitant is eliminated via interaction with CYP3A4, and moderately inhibits CYP3A4 and mildly induces CYP2C9. As such, aprepitant might alter the bioavailability of chemotherapeutics metabolized by CYP3A4, e.g., etoposide and cyclophosphamide. However, the available evidence, reviewed by Aapro et al., suggests that drug–drug interactions with aprepitant are not clinically relevant for most drugs [8].

A meta-analysis of three randomized controlled trials of neurokinin-1 antagonists versus placebo showed an increased risk of severe infection in adult patients receiving cisplatin based chemotherapy [9]. Details on the infections were not described in the included trials [9]. In these studies, the increased rate of infection might have been caused by an increased bioavailability of steroids due to an interaction with aprepitant [9, 10]. These results, although not directly applicable to the patients reported here, are to be taken into account in the risk assessment of future (fos) aprepitant trials.

Long-term use of aprepitant, i.e., more than 3 days, in children has been reported sporadically. Recently, Williams et al. identified aprepitant to be used for up to 12 days to decrease nausea in six children in the course of SCT [11]. Several studies have shown promising results for the use of aprepitant in adults during conditioning for SCT [3]. A total of five cases have been described using aprepitant for diabetic gastroparesis, non-diabetic gastroparesis or otherwise unexplained refractory nausea, for up to 18 months [12–15]. A 4-week randomized controlled trial of aprepitant versus placebo in patients with chronic nausea and vomiting due to gastroparesis failed to reach its primary endpoint, a reduction in nausea severity on a visual analog scale, but did show a reduction in the severity of nausea and vomiting using the Gastroparesis Clinical Symptom index [16].

Here, our single center experience is reported of three children who, in the course of allogeneic SCT, received

successful and well tolerated long-term off-label treatment with aprepitant for symptoms of nausea and vomiting attributed to gastroparesis. To the best of our knowledge, this is the first report on such extended use of aprepitant in children. The long-term use of aprepitant requires further investigation for improved control of nausea and emesis in pediatric stem cell recipients.

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Compliance with ethical standards

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

Informed consent Parental informed consent for all patients has been obtained.

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