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Infusion Site Reactions:

Classification in the setting of fosaprepitant administration with chemotherapy

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Abstract

BACKGROUND: Studies report a wide range of incidence and severity of infusion site adverse events (ISAEs) following fosaprepitant administration.

OBJECTIVES: The purposes of this study were

(a) to determine the incidence of suspected extravasation in patients with cancer receiving fosaprepitant infusions with chemotherapy and

(b) to determine whether the documented signs, symptoms, and management strategies aligned with the diagnostic criteria for extravasation versus non-extravasation ISAEs.

METHODS: Electronic health records were used to identify patients who received fosaprepitant infusion with chemotherapy and had documentation for suspected extravasation. Chart reviews were conducted for a sample of patients to determine whether documentation was consistent with extravasation.

FINDINGS: About 3% (n = 460 of 15,667) of patients who received fosaprepitant had documentation for suspected extravasation. Among a random sample of patients (N = 110) with a suspected extravasation, 6% (n = 6) had documentation consistent with extravasation.

Keywords

fosaprepitant; antiemetic agents; vesicant chemotherapy; extravasation

CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING is a common adverse event that can negatively affect a patient's quality of life and result in poor adherence or discontinuation of treatment (Schwartzberg, 2018). Oncology nurses frequently administer highly emetogenic chemotherapeutic agents to patients. To prevent nausea and vomiting, patients on emetogenic chemotherapy receive a variety of prophylactic antinausea regimens involving a combination of many drugs, such as palonosetron administered via IV push,

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dexamethasone administered via IV push bolus (IVPB), fosaprepitant administered via IVPB, or aprepitant administered orally (Aapro et al., 2015). Fosaprepitant and aprepitant both prevent nausea and vomiting in the delayed setting up to two weeks postchemotherapy and were shown in a randomized clinical trial to have similar efficacy (Grunberg et al., 2011).

In response to issues with patient adherence and insurance coverage of the oral preparation, aprepitant, the authors' National Cancer Institute (NCI)-designated comprehensive cancer center changed its standard practice to IV administration of fosaprepitant in 2013. After this practice change, nurses identified an increased incidence of infusion site adverse events (ISAEs), as evidenced by increases in erythema and swelling noted upon assessment, patient use of call bells to report pain, use of warm packs to alleviate symptoms, and patient reports of pain, swelling, and redness during post-treatment telephone calls (A. Segna, personal communication, July 24, 2017).

Fosaprepitant infusion has known side effects, including fatigue, diarrhea, neutropenia, asthenia, anemia, peripheral neuropathy, leukopenia, dyspepsia, urinary tract infection, and pain in the extremity (Merck, 2016). In addition, several studies (see Table 1) have reported that, for fosaprepitant infusion delivered via peripheral IV, the incidence of ISAEs is much higher than the 2.2%–3% reported in the package insert and the 2.7% reported in a large trial of 2,247 patients (Grunberg et al., 2011; Merck, 2016). These studies reported an ISAE incidence that ranged from 6% to as high as 67% in patient populations who were treated with a variety of chemotherapeutic agents (Chau et al., 2019; GonÇalves et al., 2017; Hegerova et al., 2014; Leal et al., 2014; Lundberg et al., 2014; Sato et al., 2014). ISAEs occur when drugs leak outside the vein, causing symptoms such as infusion site pain, erythema, swelling, and/or phlebitis to the site. The administration of irritant drugs can cause temporary aching, tightness, and phlebitis along the vein or at the injection site with or without a local inflammatory reaction; with vesicant drugs, there can be blistering and tissue necrosis requiring wound debridement, skin grafting, or other surgical intervention (Schulmeister, 2011).

Reports of ISAEs associated with peripheral IV administration of fosaprepitant are minor, corresponding to grade 1 or 2 on the Common Terminology Criteria for Adverse Events five-point grading scale (Chau et al., 2019; NCI, 2017). However, local data from the authors' institution indicated a higher-than-expected number of patients being followed for suspected extravasations, which are more severe events requiring different clinical management and greater likelihood of long-term morbidity.

The primary aim of the current study was to determine the incidence of suspected extravasation in a large cohort of patients with cancer receiving fosaprepitant infusions with chemotherapy. The secondary aim was to determine whether the documented signs, symptoms, and management strategies aligned with the diagnostic criteria for extravasation versus non-extravasation ISAEs.

Methods

This study was reviewed and approved by the institutional review board at Memorial Sloan Kettering Cancer Center (MSKCC) in New York, New York. MSKCC is an NCI-designated comprehensive cancer center that includes a 500-bed inpatient hospital and 12 outpatient facilities that administer chemotherapy in the New York metropolitan area. All adult patients (aged 18 years or older) who received at least one infusion of fosaprepitant from July 1, 2015, through June 30, 2018, were included in the study.

Data Collection

Retrospective study data were collected from the cancer center's centralized electronic health record (EHR) database. All adult patients with orders for fosaprepitant infusion during chemotherapy were identified, and data were collected on primary cancer diagnoses, chemotherapy orders, age, and sex.

EHR reviews were performed on a random sample of about 25% of patients with suspected extravasations to determine whether documented signs, symptoms, and management strategies were consistent with extravasation versus non-extravasation ISAEs. Two master's-prepared oncology nurses performed the chart review using a standardized data collection form. The documents reviewed included Nursing Extravasation Assessment initial note and follow-up notes, Patient Education Documentation notes, Licensed Independent Practitioner notes, and Reporting to Improve Safety and Quality reports (the institution's event-reporting system). To determine the incidence of suspected extravasation in this cohort, patients were identified if there was documentation in a nursing extravasation assessment note in the EHR. Per institutional policy, nurses document signs and symptoms of extravasation in the Nursing Extravasation Assessment note, which includes a combination of checkboxes and free-text fields. ISAEs were classified as extravasation events if at least one of the following signs, symptoms, or management strategies were documented: blistering, oozing, sloughing, necrosis, debridement, ulceration, or weeping. In the absence of these terms, events were classified as non-extravasation ISAEs, which can include pain, burning, swelling, redness, change in skin temperature/sensation, phlebitis, decreased range of motion, or decreased IV flow rate/blood return (see Figure 1).

Data Analysis

The proportion of patients with documentation of a suspected extravasation following fosaprepitant infusion with chemotherapy was calculated for all patients meeting the inclusion criteria. The proportion of patients with documented signs, symptoms, and management strategies associated with extravasation versus non-extravasation ISAEs was calculated among the sample of patients with suspected extravasation. The data collected consisted of patient characteristics (e.g., age, sex, diagnosis, chemotherapy); the frequency of documented signs, symptoms, and management strategies; and the proportion of patients requiring more than 21 days of follow-up.

Results

A total of 15,667 patients received at least one IV fosaprepitant infusion with chemotherapy during the study period. Of those, 460 patients (3%) had documentation for suspected extravasation.

EHR reviews were conducted for a random sample of 110 of 460 patients with suspected extravasation. All patients in this sample received fosaprepitant via peripheral IV. The sample included 65 women and 45 men. The median age was 67 years (range = 21–89). The most common primary cancer diagnoses were lung (n = 21), breast (n = 11), endometrial (n = 11), ovarian (n = 10), prostate (n = 6), sarcoma (n = 6), and lymphoma (n = 5). The most common chemotherapy drugs administered were carboplatin (n = 15), paclitaxel/carboplatin (n = 15), etoposide (n = 15), paclitaxel (n = 13), gemcitabine (n = 10), doxorubicin (n = 6), and docetaxel (n = 5).

The incidence of documented signs, symptoms, and management strategies of extravasation and non-extravasation ISAEs is reflected in Table 2. A total of six patients had documentation suggesting an extravasation event, with four having documented blistering and two having documented oozing. None of the patients in this sample had documentation of sloughing, necrosis, debridement, ulceration, or weeping. The six patients with signs of extravasation ranged in age from 51 to 86 years, represented a range of cancer diagnoses (i.e., ovarian, prostate, breast, endometrial, sarcoma, and lung) and received a range of chemotherapy agents (i.e., carboplatin, paclitaxel/carboplatin, etoposide, paclitaxel, gemcitabine, doxorubicin, and docetaxel).

Of note, carboplatin and etoposide are not classified as vesicant agents (Jackson-Rose et al., 2017).

The most common documented signs and symptoms overall were swelling (n = 90), redness (n = 35), decreased blood return (n = 35), and changes in skin temperature (n = 32). The number of documented signs and symptoms ranged from one to five, with the majority of patients (n = 87, 79%) having at least two. Twenty-one patients (19%) had an ISAE requiring follow-up exceeding 21 days.

Discussion

Previous studies raised concerns about the high prevalence of ISAEs following fosaprepitant administration, particularly when peripheral IV access is used (Chau et al., 2019; Gonçalves et al., 2017; Hegerova et al., 2015; Leal et al., 2014; Lundberg et al., 2014; Sato et al., 2014). Although ISAEs can cause acute discomfort and distress for patients, extravasations and resulting tissue necrosis can cause severe long-term injury, including chronic pain, neuropathy, loss of function or mobility, and cosmetic deformity (Al-Benna et al., 2013). Therefore, distinguishing between extravasation and non-extravasation ISAE incidence is important for decision making around fosaprepitant prescribing at the institutional and patient level.

Making such distinctions can be challenging, however, as clinical presentations vary from patient to patient and observational methods of identifying extravasation are subjective and have poor reliability (Matsui et al., 2017). Distinguishing extravasation from non-extravasation ISAEs is challenging in clinical documentation because all signs and symptoms, regardless of initial severity, must be followed as possible extravasation events to mitigate potential harm to patients (Gonzalez, 2013).

The findings of this study suggest that the vast majority of patients who are followed for suspected extravasation do not exhibit signs and symptoms consistent with this type of ISAE. Still, in this cohort of patients who received fosaprepitant with chemotherapy, the incidence of extravasation was higher than what has been reported for the general population of patients receiving chemotherapy (Jackson-Rose et al., 2017; Rodriguez-Reyes et al., 2018; Sakaida et al., 2014). Estimating from the incidence of extravasation in the sample of patients included in this chart review, incidence of extravasation in the study cohort is about 0.16%. This is comparable, though slightly higher, than the 0.04%–0.09% reported in other studies (Jackson-Rose et al., 2017; Rodriguez-Reyes et al., 2018; Sakaida et al., 2014). This may be from differences in methodology (e.g., how extravasations were identified, the definitions by which they were classified), differences in institutional practices regarding extravasation prevention (e.g., nurse education, training, and experience; chemotherapy administration protocols), differences in methods of administration (e.g., prevalence of peripheral IV versus central venous access devices [CVADs] and device types), differences in the underlying patient population (e.g., type of cancer, type of chemotherapy, treatment history), the role of chance in sampling, or the fact that all members of this cohort received fosaprepitant with chemotherapy. Overall, the prevalence of any type of ISAE following fosaprepitant was consistent with the 2%–3% reported by the drug's manufacturer (Merck, 2016).

Limitations

A limitation of this study is that it was not possible to determine the route of administration (i.e., peripheral IV versus CVAD) for all patients; therefore, it was not possible to assess whether route of administration is associated with ISAEs, as suggested in previous studies (Chau et al., 2019; Gonçalves et al., 2017; Hegerova et al., 2014; Leal et al., 2014; Lundberg et al., 2014; Sato et al., 2014). Another limitation was the lack of valid and reliable methods for distinguishing extravasation from non-extravasation ISAEs, making it difficult to compare extravasation incidence across other studies and settings (Matsui et al., 2017). In the absence of clear, published assessment standards, this study used an evidence-based institutional nursing policy for classifying extravasation.

Implications for Nursing

Nurses must remain vigilant when administering cytotoxic agents and closely monitor patients for any signs of ISAEs. Although these events can occur with any treatment, patients receiving fosaprepitant in addition to chemotherapy may be at an increased risk for extravasation. Nurses should adhere to the American Society of Clinical Oncology/ Oncology Nursing Society Chemotherapy Administration Safety Standards for patients

receiving fosaprepitant (Neuss et al., 2017). Nurses must be familiar with the signs, symptoms, and management strategies of extravasation because prompt action is critical to prevent further tissue damage during a suspected extravasation. Nurses should review the common ISAEs with their patients and instruct them to call if they note any unusual changes at the infusion site.

Conclusion

Although the incidence of extravasation in this cohort of patients receiving fosaprepitant was slightly higher than what has been reported in the general population of patients receiving chemotherapy, 94% of patients followed for suspected extravasations did not have documentation of the characteristics associated with an extravasation event. Extravasation remains a rare occurrence among the population of patients receiving fosaprepitant infusion with chemotherapy.

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IMPLICATIONS FOR PRACTICE

- Be aware that fosaprepitant may increase the risk of extravasation and other infusion site adverse events despite that the incidence of extravasation following fosaprepitant infusion with chemotherapy is low.
- Monitor for extravasation in patients receiving fosaprepitant with irritant or vesicant chemotherapy.
- Learn how to distinguish between extravasation and non-extravasation infusion site adverse events to determine appropriate management, follow-up, patient education, and clinical documentation.

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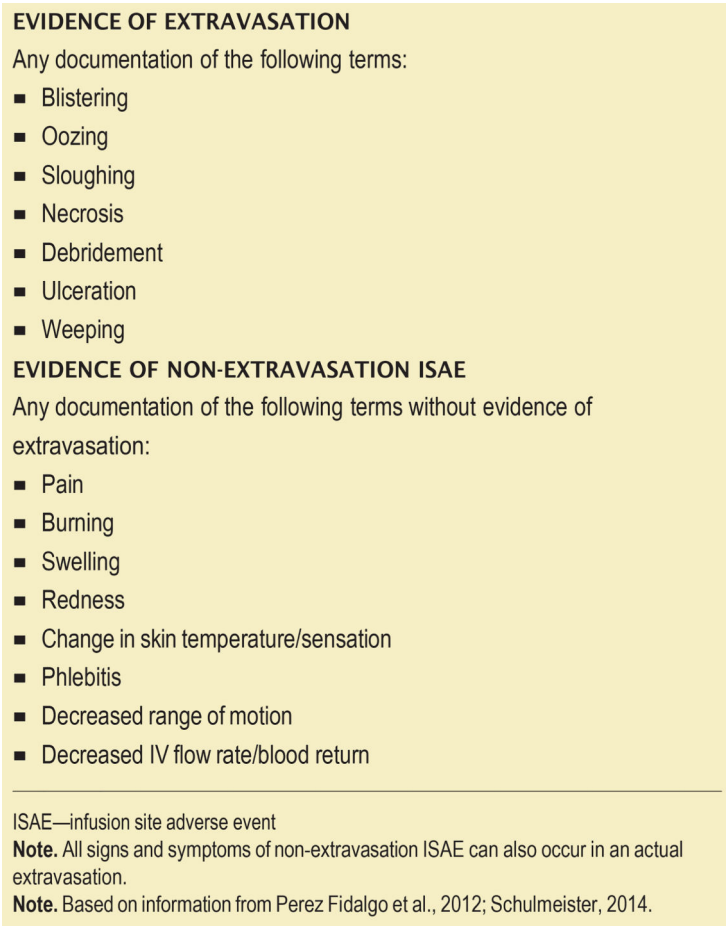

FIGURE 1.
EVIDENCE OF EXTRAVASATION VERSUS NON-EXTRAVASATION ISAEs

TABLE 1

STUDIES OF ISAEs IN PATIENTS RECEIVING FOSAPREPITANT VIA PERIPHERAL IV ACCESS

STUDY	SAMPLE AND PATIENT POPULATION	ISAE INCIDENCE	POSSIBLE RISK FACTORS FOR ISAE IDENTIFIED
Chau et al., 2019	122 patients receiving any outpatient chemotherapy (285 infusions)	6%	Concentration of fosaprepitant; length of infusion
Gonçalves et al., 2017	57 patients receiving IV fosaprepitant (105 infusions)	40%	First time administration of fosaprepitant older age; IV placed in hand or wrist
Hegerova et al., 2014	64 patients with breast cancer	9%	Doxorubicin/cyclophosphamide administration
Leal et al., 2014	148 patients receiving doxorubicin/ cydophosphamide	35%	–
Lundberg et al., 2014	150 patients receiving any outpatient chemotherapy (333 infusions)	15%	IV placed in hand; IV fluid rate less than 100 ml per hour; younger age
Sato et al., 2014	56 patients receiving anthracycline (159 infusions)	67%	Doxorubicin/cyclophosphamide administration

ISAE–infusion site adverse event

TABLE 2

PREVALENCE OF SIGNS AND SYMPTOMS OF ISAEs FOLLOWING ADMINISTRATION OF IV FOSAPREPITANT (N = 110)

SIGN OR SYMPTOM	n	%
Evidence of extravasation		
Blistering	4	4
Oozing	2	2
Sloughing	–	–
Necrosis	–	–
Debridement	–	–
Ulceration	–	–
Weeping	–	–
Signs and symptoms consistent with extravasation or non-extravasation ISAEs		
Swelling	90	82
Redness	35	32
Decreased blood return	35	32
Change in skin temperature	32	29
Decreased flow rate	22	20
Burning	17	16
Pain	13	12
Decreased range of motion	6	6
Phlebitis	–	–

ISAE–infusion site adverse event