Cisplatin-Based Therapy and CINV
Optimal antiemetics during germ cell testicular cancer treatment

Meghan Mastrangelo, MSN, AGACNP-BC

BACKGROUND: Cisplatin-based chemotherapy regimens are the backbone of chemotherapy for germ cell testicular cancer. Cisplatin is administered for five days, causing an overlap of acute and delayed chemotherapy-induced nausea and vomiting (CINV). Although CINV is widely researched, studies involving multiday chemotherapy regimens are limited.

OBJECTIVES: This article synthesizes the research in antiemetics used in multiday cisplatin-based chemotherapy regimens and provides recommendations to optimize antiemetic therapy.

METHODS: A literature review was conducted for articles examining antiemetics in multiday cisplatin-based chemotherapy regimens. Results were synthesized, and findings were applied to existing antiemetic strategies.

FINDINGS: Although an optimal regimen has not been identified, patients receiving multiday cisplatin chemotherapy should have an antiemetic administered on each day of chemotherapy and two to three days after chemotherapy. Antiemetics should include an NK1 antagonist, 5-HT3 receptor antagonist, and dexamethasone.

THE QUALITY OF LIFE OF PATIENTS WITH CANCER can be negatively affected by chemotherapy-induced nausea and vomiting (CINV) and further complicate their ability to tolerate chemotherapy and adhere to planned chemotherapy regimens. Cisplatin is categorized as highly emetogenic chemotherapy (HEC), with 90% frequency of emesis if antiemetics are not administered (National Comprehensive Cancer Network [NCCN], 2017). According to Lorusso (2016), nausea remains the side effect with the highest impact on quality of life among patients undergoing chemotherapy. Uncontrolled nausea and vomiting can lead to dehydration, electrolyte imbalances, and nutritional deficits (NCCN, 2017). The most significant risk factor associated with CINV is the chemotherapeutic agent being used to treat the cancer. CINV is classified into three groups based on time of onset of nausea and vomiting: anticipatory, acute, and delayed (Hesketh, 2017). Anticipatory emesis is a learned response that occurs in patients who experienced uncontrolled CINV in previous chemotherapy cycles. Acute emesis occurs in the first 24 hours after chemotherapy and typically begins within hours of treatment if appropriate antiemetics are not administered. Delayed emesis is any episode of emesis that begins more than 24 hours after chemotherapy and is most common with high-dose cisplatin chemotherapy. Understanding the different timing of nausea and vomiting is crucial to optimizing antiemetic therapy. Because chemotherapy is given with curative intent for patients with germ cell testicular cancer, avoiding any potential treatment delays from dehydration, poor performance status, or poor compliance with chemotherapy is critical.

Cisplatin-based combination chemotherapy regimens have resulted in a cure rate of greater than 90% for patients with germ cell testicular cancer (Chabner et al., 2011). Cisplatin is classified as HEC regardless of dose; therefore, any regimens containing cisplatin chemotherapy require proper antiemetics to prevent CINV (NCCN, 2017). The previously standard antiemetic regimen consisting of a serotonin (5-hydroxytryptamine) receptor antagonist (5-HT3RA) and dexamethasone results in prevention of nausea and vomiting episodes in fewer than 60% of patients (Hamada et al., 2014). Managing CINV during multiday cisplatin regimens is more challenging because patients are vulnerable to nausea and vomiting on all five days of therapy and at risk of overlapping acute and delayed nausea throughout their...
treatment (Ranganath, Einhorn, & Albany, 2015). CINV peaks from days 3–5 of chemotherapy, when acute and delayed nausea overlap (Olver et al., 2013).

In addition, preventing the development of anticipatory nausea and vomiting is important for compliance, quality of life, and maintaining adequate hydration and nutritional status throughout chemotherapy. Preventing CINV at first chemotherapy cycle is crucial because the majority of patients who are emesis-free at their first treatment remain so for subsequent cycles (Hesketh, 2017). In a study of patients with germ cell testicular cancer receiving five-day BEP chemotherapy, which consists of bleomycin, cisplatin, and etoposide, more than half experienced grade 3 or worse CINV at some point during chemotherapy despite antiemetics (Olver et al., 2013).

Pathophysiology
Emesis occurs as a result of the activation of a multistep pathway of various receptors in the brain and gastrointestinal tract. Chemotherapy activates receptors that are located in the gastrointestinal tract, the chemoreceptor trigger zone, and the vomiting center of the brain. Each pathway of the brain involved with nausea and vomiting is innervated differently, which has led to different receptor targets for antiemetic drugs (Hesketh, 2017). Three specific neurotransmitters have been associated with CINV: dopamine, serotonin (5-HT₃), and substance P (Hesketh, 2017). Antiemetic medications target these neurotransmitters to antagonize their action. Each drug blocks different pathways along the process, or works synergistically with other antiemetics to improve antiemetic effect, as seen with dexamethasone and 5-HT₃RAs (NCCN, 2017). As each drug targets a specific neurotransmitter, the drugs work differently in the body and are best used in combination for maximum benefit for coverage of acute and delayed emesis. It has been well established that antiemetic drugs block only one receptor type; therefore, no single antiemetic medication can provide complete prevention of all phases of CINV (NCCN, 2017).

Nausea has become more common than vomiting because of the improvements in antiemetics (NCCN, 2017). Although nausea and vomiting are related, they occur via different mechanisms. Beyond prevention of CINV, it is important to optimize appropriate breakthrough medications to help control CINV if it should present despite antiemetic medications.

Research
As noted in the NCCN (2017) guidelines for antiemesis, research regarding antiemetic regimens in multiday chemotherapy is limited. The studies reviewed in this article provide some insight into the challenges of managing multiday cisplatin-based chemotherapy CINV risk and reveal the lack of knowledge in optimal regimens for these patients. However, synthesis of the available data, as well as applying knowledge regarding CINV management, allows for an outline of principles to guide decisions and direct future research as CINV medications continue to evolve.

Several databases were searched, including PubMed and Embase, for studies evaluating CINV during multiday cisplatin-based chemotherapy regimens for germ cell testicular cancer. References for each study found were evaluated for additional resources, as were guidelines from the American Society of Clinical Oncology (ASCO). One study was reviewed but not included because it only evaluated three-day cisplatin regimens. Ultimately, six studies and two review articles were included in the literature review for the current article. Each research study looked at a primary endpoint of complete response (CR), meaning no episodes of emesis and no use of rescue medications. In addition, studies regarding optimal 5-HT₃RA medications and other antiemetic principles were reviewed to help guide ultimate management recommendations.

Table 1 summarizes the antiemetic regimen evaluated in each study and includes CR rates. Each study looked at a five-day cisplatin-based chemotherapy regimen for patients with germ cell testicular cancer. Studies varied regarding which antiemetics were used. In these studies, rates of emesis, rescue medication use, and incidence of nausea were tracked via patient self-report journals. Major limitations of the studies included small sample sizes and lack of a control group. A study by Hamada et al. (2014) evaluated a combination regimen of palonosetron, aprepitant, and dexamethasone for CINV prevention and had the highest rates of CR among the studies available. However, the study had a small sample size of only 30 patients and had no control group related to the low incidence of testicular cancer in Japan. In addition, the approved dosing of palonosetron in Japan is 0.25 mg, which leads to difficulty applying the study findings in the United States, where the approved dose is 0.25 mg. However, the high rates of CR seen in 90% of patients during cycle 1, 82% in cycle 2, and 78% in cycle 3, which are significantly higher than the historic control of 60%, indicate a possible area for future research in palonosetron dosing (Hamada et al., 2014).
Adra et al. (2016) found a much lower CR rate with fosaprepitant than with aprepitant; although this could be attributed to difference in efficacy or dosing regimens between the oral aprepitant and IV fosaprepitant, a few variables in the study could contribute to the large difference in CR rates. Of note, 15% of the patient logs were not returned. In addition, fosaprepitant was not given until days 3 and 5; therefore, it can be argued that the neurokinin-1 (NK₁) prevention of delayed nausea was not initiated early enough during the chemotherapy protocol to properly prevent delayed nausea. By comparison, Albany et al. (2012) and Hamada et al. (2014) administered aprepitant starting on day 1 or 2 of chemotherapy. A major limitation of the studies is reliance on patients to properly document and return study journals. Most studies referenced Einhorn et al.'s (2007) study regarding palonosetron plus dexamethasone as the historic control for rates of CR, which noted prevention of nausea and vomiting episodes in fewer than 60% of patients. Rescue medications used for breakthrough nausea and vomiting varied in each study and were often determined at the discretion of the oncology team.

Across all studies, nausea and vomiting peaked between days 3–5, with most patients reporting the highest levels of nausea and vomiting on day 4. Two of the studies with the lowest CR rates (e.g., Adra et al., 2016; Einhorn et al., 2007) had no antiemetic

### Table 1

**Antiemetic Regimen by Day and Study**

<table>
<thead>
<tr>
<th>Study</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 6</th>
<th>Day 7</th>
<th>Day 8</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adra et al., 2016</td>
<td>Decadron 20 mg PO, palonosetron 0.25 mg IV</td>
<td>Decadron 20 mg PO</td>
<td>Fosaprepitant 150 mg IV, palonosetron 0.25 mg IV</td>
<td>—</td>
<td>Fosaprepitant 150 mg IV, palonosetron 0.25 mg IV</td>
<td>Decadron 4 mg PO BID</td>
<td>Decadron 4 mg PO BID</td>
<td>Decadron 4 mg PO BID</td>
<td>CR of 24% in days 1–8; CR of 50% in acute phase and 46% in delayed phase</td>
</tr>
<tr>
<td>Albany et al., 2012</td>
<td>Decadron 20 mg PO plus 5-HT₃RA (not aloxi)</td>
<td>Aprepitant 125 mg or placebo, 5-HT₃RA</td>
<td>Aprepitant 80 mg or placebo, 5-HT₃RA</td>
<td>Aprepitant 80 mg or placebo, 5-HT₃RA</td>
<td>Aprepitant 80 mg or placebo, 5-HT₃RA</td>
<td>Aprepitant 80 mg decarboxylated for delayed nausea was 66% in acute phase, 63% in delayed phase</td>
<td>Placebo cycle: CR of 15% in acute phase and 55% in delayed phase</td>
<td>CR in days 1–5, 34%; CR in days 6–9, 61%; no emetic episodes days 1–5, 51%</td>
<td></td>
</tr>
<tr>
<td>Einhorn et al., 2007</td>
<td>Palonosetron 0.25 mg IV, decadron 20 mg IV</td>
<td>Decadron 20 mg IV</td>
<td>Palonosetron 0.25 mg IV</td>
<td>—</td>
<td>Palonosetron 0.25 mg IV</td>
<td>Decadron 8 mg PO</td>
<td>Decadron 8 mg PO</td>
<td>Decadron 4 mg PO BID</td>
<td>CR in days 1–5, 54%; CR in days 6–9, 61%; no emetic episodes days 1–5, 51%</td>
</tr>
<tr>
<td>Hamada et al., 2014</td>
<td>Palonosetron 0.75 mg IV, aprepitant 125 mg PO, decarboxylated 12 mg IV</td>
<td>Aprepitant 80 mg PO, decarboxylated 9 mg IV</td>
<td>Aprepitant 80 mg PO, decarboxylated 9 mg IV</td>
<td>Aprepitant 80 mg PO, decarboxylated 9 mg IV</td>
<td>Aprepitant 80 mg PO, decarboxylated 9 mg IV</td>
<td>Decadron 9 mg IV</td>
<td>Decadron 9 mg IV</td>
<td>Decadron 9 mg IV</td>
<td>Overall CR of 90% in cycle 1, 82% in cycle 2, 78% in cycle 3; incidence of nausea peaked on days 4–6, with 50% of patients reporting nausea</td>
</tr>
<tr>
<td>Jordan et al., 2009</td>
<td>Aprepitant 80 mg PO, granisetron 1 mg IV, decarboxylated 8 mg IV</td>
<td>Aprepitant 80 mg PO, granisetron 1 mg IV, decarboxylated 8 mg IV</td>
<td>Aprepitant 80 mg PO, granisetron 1 mg IV, decarboxylated 8 mg IV</td>
<td>Aprepitant 80 mg PO, granisetron 1 mg IV, decarboxylated 8 mg IV</td>
<td>Aprepitant 80 mg PO, granisetron 1 mg IV, decarboxylated 8 mg IV</td>
<td>Aprepitant 80 mg PO, decarboxylated 8 mg PO</td>
<td>—</td>
<td>—</td>
<td>HEC CR was 66% in acute phase, 68% in delayed phase, and 58% overall; nausea reported in 24% of HEC group</td>
</tr>
<tr>
<td>Oliver et al., 2013</td>
<td>Aprepitant 125 mg PO, 5-HT₃RA, decarboxylated 8 mg PO</td>
<td>Aprepitant 80 mg PO, 5-HT₃RA, decarboxylated 8 mg PO</td>
<td>Aprepitant 80 mg PO, 5-HT₃RA, decarboxylated 8 mg PO</td>
<td>Aprepitant 80 mg PO, 5-HT₃RA, decarboxylated 8 mg PO</td>
<td>Aprepitant 80 mg PO, 5-HT₃RA, decarboxylated 8 mg PO</td>
<td>Decadron 8 mg PO</td>
<td>Decadron 8 mg PO</td>
<td>—</td>
<td>CR in days 1–7, 41% for cycle 1, 53% for cycle 2, 45% for cycle 3, and 56% for cycle 4</td>
</tr>
</tbody>
</table>

CR—complete response; HEC—highly emetogenic chemotherapy; RA—receptor antagonists
medications given on day 4. Despite the fact that medications such as palonosetron and aprepitant have a longer half-life and are supposed to provide multiple days’ worth of antiemesis coverage, it is reasonable to deduce that aggressive antiemetic medications should be given on days 3–5 because of the high risk of acute and delayed CINV on these days. Olver et al.’s (2013) study looked at aprepitant on days 1–5 in addition to decadron and a 5-HT,RA. The study was conducted in Australia, so it used their standard 5-HT,RA agents granisetron or tropisetron. Emesis was well controlled, with 82% of patients reporting no emesis on days 1–7. However, nausea was poorly controlled, with only 27% of patients reporting no nausea on days 1–7 (Olver et al., 2013).

**Future Research**

Olanzapine, an antipsychotic medication, has been studied in single-day HEC regimens with promising results in CINV prevention. Olanzapine blocks multiple neurotransmitters, including dopamine and serotonin, resulting in prevention of nausea and vomiting (Navari et al., 2016). The drug does have side effects, including sedation and weight gain; therefore, establishing its safety profile in multiday chemotherapy regimens is important. The study conducted by Navari et al. (2016) evaluated the addition of olanzapine on days 1–4 to the current standard regimen for single-day HEC (consisting of a 5-HT,RA, NK, antagonist, and dexamethasone) and used a placebo control group to evaluate effectiveness of olanzapine. The study used patient reports of no nausea as the primary endpoint, and patients reported higher rates of no nausea in the olanzapine group across acute, delayed, and overall periods. CR was also evaluated, with 64% of the olanzapine group reporting CR versus 41% of the control group (Navari et al., 2016). Establishing the safety and efficacy of adding olanzapine to multiday cisplatin regimens is warranted.

**Table 2.**

**ANTIEMETIC OPTIONS DURING CHEMOTHERAPY**

<table>
<thead>
<tr>
<th>DRUG CLASS</th>
<th>MEDICATION OPTIONS</th>
<th>KEY SIDE EFFECTS</th>
</tr>
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<tbody>
<tr>
<td>5-HT,RA</td>
<td>Ondansetron, palonosetron, granisetron, tropisetron</td>
<td>Headache, constipation, QTc prolongation</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>Olanzapine, prochlorperazine, haloperidol</td>
<td>EPS, sedation, insomnia</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Lorazepam</td>
<td>Sedation, confusion</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Dexamethasone</td>
<td>Hyperglycemia, insomnia, bone necrosis</td>
</tr>
<tr>
<td>NK, antagonist</td>
<td>Aprepitant, fosaprepitant</td>
<td>Drug interactions</td>
</tr>
</tbody>
</table>

5-HT—5-hydroxytryptamine; EPS—extrapyramidal symptoms; NK1—neurokinin-1; RA—receptor antagonists

*Note.* Based on information from National Comprehensive Cancer Network, 2017.

**Recommendations**

Although additional research is needed to identify the optimal dosing schedule, medications used, and possible addition of olanzapine to antiemetic regimens, the existing studies reveal patterns and improvements in CINV prevention that can help guide clinicians in prescribing antiemetics for multiday cisplatin-based chemotherapy regimens for treatment of germ cell testicular cancer. Cisplatin is considered HEC at any dose and, therefore, principles of CINV prevention should follow HEC principles. These principles are outlined in various antiemetic guidelines, including NCCN, American Society of Clinical Oncology (ASCO), and Multinational Association of Supportive Care in Cancer (MASCC). This includes an NK, antagonist, 5-HT,RA, and dexamethasone. Research is not yet available regarding safety and efficacy of newer agents, such as olanzapine; until data are available, newer agents should not be used in multiday cisplatin-based chemotherapy CINV prevention.

Based on the studies reviewed, CINV incidence is greatest on days 3–5 when acute and delayed nausea overlap. The studies with the lowest CR rates had no antiemetics administered on day 4, and studies with highest CR rates had at least one antiemetic administered on each day of chemotherapy. Therefore, based on a clinical interpretation of the results of these studies, the recommendation is administration of at least one antiemetic on each day of chemotherapy (see Table 2) and to optimize antiemetic administration through days 3–5 for adequate coverage. NK, antagonists, such as fosaprepitant, have been shown to have the largest benefit in preventing delayed CINV (NCCN, 2017). In Adra et al.’s (2016) study of palonosetron, dexamethasone, and fosaprepitant, the fosaprepitant was not administered until day 3 of chemotherapy, which could contribute to the poor CR rates in the study because delayed nausea begins 24 hours after chemotherapy. Administering fosaprepitant prior to chemotherapy on day 1 would potentially provide better prevention of delayed CINV.

The studies that had the highest rates of CR were conducted by Hamada et al. (2014) and Jordan et al. (2009) and looked at triple antiemetic combination CINV prevention. Hamada et al.’s (2014) study was conducted in Japan where the approved dose of palonosetron is 0.75 mg, but given the fact that it has now been established that it is safe to administer repeat dosing of palonosetron 0.25 mg, this antiemetic regimen may be an option for patients treated in the United States. In addition, aprepitant was administered on days 1–5, 125 mg on day 1 and 80 mg days 2–5 (Hamada et al., 2014). Jordan et al.’s (2009) study looked at aprepitant, granisetron, and dexamethasone as triple antiemetic premedication. The study gave 125 mg aprepitant on day 1 and 80 mg aprepitant on days 2–7. CINV was well controlled without increased risk of toxicities from chemotherapy (Jordan et al., 2009). To date, aprepitant is approved to be administered on days 1–3, with 125 mg on day 1 prior to chemotherapy and 80
mg on days 2 and 3. Based on the limited research available, the NCCN (2017) guidelines note that dosing of aprepitant 80 mg beyond day 3 may be safely administered without risk of toxicity.

Palonosetron has proven to be safe to administer repeat dosing by various studies; therefore, if palonosetron is the 5-HT,RA of choice, it should be administered on days 1 and 3 to provide adequate coverage through the entire chemotherapy regimen (Eisenberg et al., 2003; Hunt, Gallagher, Cullen, & Shah, 2005). If ondansetron is used as the 5-HT,RA, its administration is prior to chemotherapy on each treatment day.

Long-term steroid use places patients at risk for hyperglycemia and avascular necrosis. However, the use of steroids in antiemetic regimens is well established, so cautious use of steroids, including limiting dosing and duration, is critical to mitigate toxicity risk (Ranganath et al., 2015). The optimal dosing of dexamethasone remains to be determined, but dexamethasone has a clear benefit in preventing CINV. When used in combination with fosaprepitant or aprepitant, dosing of dexamethasone should be decreased related to its effects on the CYP3A4 pathway, which leads to higher serum concentration of dexamethasone (Ranganath et al., 2015). According to the studies reviewed for the current article, the regimens with highest rates of CR included dexamethasone on all days of chemotherapy and at least two days after chemotherapy completion.

For HEC regimens, the NCCN (2017) guidelines recommend administering dexamethasone once daily throughout all days of chemotherapy and continuing dexamethasone for an additional 2–3 days after chemotherapy is complete. Although the guidelines do not recommend a specific dose for each day, most of the available studies used a dexamethasone dose of 4–8 mg after chemotherapy. The MASCC guidelines recommend that all patients on multiday cisplatin receive a 5-HT,RA, dexamethasone, and aprepitant for antiemesis (Ranganath et al., 2015). However, the guidelines do not indicate a dosing schedule for these medications. Similarly, the ASCO guidelines (Hekseth et al., 2017) recommend patients receive a combination of an NK, antagonist, 5-HT,RA, and dexamethasone, again without a specific dosing schedule. For patients with a history of diabetes, severe gastroesophageal reflux disease, or sleep disturbances, clinicians are advised to administer dexamethasone dosing in the morning to avoid exacerbating insomnia.

The addition of an NK, antagonist has been shown to greatly improve CINV prevention in single-day chemotherapy regimens. Using an NK, antagonist in combination with a 5-HT,RA and dexamethasone has been studied and shown to improve CINV control (NCCN, 2017). Based on limited study data, clinicians are advised that aprepitant is more effective than fosaprepitant for multiday chemotherapy regimens and is safe to administer beyond day 3 of chemotherapy. Until better research can be conducted, ideally as a multi-arm, randomized, controlled trial comparing fosaprepitant to aprepitant using the same dosing schedule for other drugs in the regimen, aprepitant appears to be superior to fosaprepitant for multiday cisplatin-based chemotherapy regimens. Clinicians are advised to watch for drug interactions, and dexamethasone dosing should be decreased on days administered with an NK, antagonist (Ranganath et al., 2015). Future research should also include evaluating the safety and efficacy of repeat dosing of fosaprepitant; data on repeat dosing are currently not available.

Rescue Medications
Although most studies had the primary outcome of no emesis and no rescue medicine use, it is important to consider optimal rescue medication principles to improve patient quality of life and CINV control throughout chemotherapy treatment. A few key principles should be used to optimize breakthrough medication use. First, providers should add a medication from a different drug class than the original regimen. This could include adding medications, such as lorazepam, olanzapine, or prochlorperazine, that were not part of the initial antiemetic regimen.

In addition, after receiving palonosetron, use of breakthrough 5-HT,RA medications, such as ondansetron, provides little relief of delayed CINV; therefore, rescue medications should be from a different medication class (NCCN, 2017). If breakthrough medications provide control of nausea and vomiting, the breakthrough medications should be continued as scheduled medications rather than as needed (NCCN, 2017). Prior to the next cycle of chemotherapy, providers must address CINV incidence and consider adding medications or adjusting antiemetics if nausea and vomiting was poorly controlled. If CINV was poorly controlled, consider addition of an antiemetic from a different drug class, administer dexamethasone an additional two days after chemotherapy, or optimize dosing of agents used to ensure optimal CINV prevention.

Limitations
Research, to date, has included small studies with limited sample sizes. In addition, the variability among studies in medication choices, dosage of dexamethasone, and scheduling of antiemetics makes it difficult to fully compare each study and identify an ideal regimen. Another significant limitation of the available research is the development of new antiemetic medications, including olanzapine and akynzeo. Although these agents appear
highly effective in CINV prevention, their role and optimal dosing schedule in multiday chemotherapy has not been confirmed.

**Implications for Practice**

Nurses have a crucial role in advocating for their patients to ensure optimal antiemetic therapy is being administered. By having a greater understanding of antiemetic principles and optimal medication regimens, nurses are able to ensure their patients are receiving the best CINV prevention. In addition, nurses are able to advocate to providers when a patient’s CINV has not been effectively managed and can encourage alternative antiemetics. Because no current standard antiemetic regimen has been determined, providers may not be prescribing adequate antiemetic medications for patients, and nurses can advocate for their patients and discuss the literature with providers to ensure optimal CINV prevention.

**Conclusion**

Guidelines from NCCN, ASCO, and MASCC are excellent resources to help guide protocol development and aid decision making while taking the patient’s medical history and preferences into account. However, additional research is needed for this subject. Nurses can participate in antiemetic research and identify the need for additional information to identify the optimal antiemetic regimen and dosing for multiday cisplatin-based chemotherapy regimens.

Meghan Mastrangelo, MSN, AGACNP-BC, is a nurse practitioner in the Division of Hematology/Oncology at the Hospital of the University of Pennsylvania in Philadelphia. Mastrangelo can be reached at meghan.mastrangelo@gmail.com, with copy to CJONEditor@ons.org. (Submitted July 2017. Accepted September 11, 2017.)

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**REFERENCES**


