

# Quality versus queasy: neurokinin 1 receptor antagonist use in moderately emetogenic chemotherapy

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**Background** The American Society of Clinical Oncology (ASCO) launched the Quality Oncology Practice Initiative (QOPI) program in 2010 to promote quality cancer care. The association has subsequently influenced the use of neurokinin 1 (NK-1) receptor antagonists through articles published in peer-reviewed publications and its Choosing Wisely campaign.

**Objective** To explore the rationale behind the use of NK-1 receptor antagonists in clinical practice.

**Methods** We distributed an anonymous 12-question online survey to 650 medical oncologists in 5 states, inquiring about their use of these agents. A total of 155 responses were analyzed.

**Results** QOPI-certified physicians were significantly more likely than noncertified physicians to use NK-1 receptor antagonists with moderately emetogenic regimens, including weekly cisplatin for head and neck cancer (82.6% vs 27.0%, respectively;  $P < .001$ ), cervical and bladder cancer (81.4% vs 32.7%,  $P < .001$ ), and with CHOP (cyclophosphamide, hydroxydaunorubicin, oncovin, prednisone) with or without rituxinab in lymphoma (81.4 vs 17.3%,  $P < .001$ ). The majority of QOPI-certified physicians reported using these agents for the sole purpose of maintaining QOPI certification (80.0%-86.0%). Certified physicians were also significantly more likely to appropriately prescribe NK-1 antagonists with highly emetogenic chemotherapy.

**Limitations** Responder bias; short survey that precludes detailed analysis; small sample size may limit generalizability to the field of medical oncology.

**Conclusion** Our data demonstrate that providers in QOPI-certified practices are significantly more likely than those in noncertified practices to prescribe NK-1 receptor antagonists. Certified physicians report that satisfying ASCO-QOPI requirements is their primary motivation for offering these agents.

The majority of patients treated with systemic chemotherapy will experience some form of toxicity during their treatment course. A significant percentage of those individuals will experience nausea and/or vomiting, which may provoke anxiety and reduce patient satisfaction with therapy and care and patient quality of life.<sup>1</sup> In our current chemotherapy armamentarium, platinum-based agents, particularly cisplatin, are among the most highly emetogenic. In recognition of this, Hesketh and colleagues ranked high-dose cisplatin ( $\geq 50$  mg/m<sup>2</sup>) in the highest tier (level 5) when they stratified chemotherapies by emetogenic risk.<sup>2</sup> Agents in level 5 are associated with a >90% risk of emesis. At doses of less than 50 mg/m<sup>2</sup>, cisplatin is in level 4 with an emesis frequency of 60%-90%.<sup>2</sup> In 1999, the American Society of Clinical Oncology (ASCO) introduced its first antiemetic clinical practice guide-

lines.<sup>3</sup> Through 2 subsequent iterations, cisplatin has consistently remained in the highest emetic risk category regardless of the selected dose.<sup>4,5</sup> Although prophylactic 5-hydroxytryptamine (5-HT<sub>3</sub>) antagonists and corticosteroids were initially recommended for patients in this high-risk category, updated guidelines from 2006 and 2011 recommend the addition of the neurokinin 1 (NK-1) receptor antagonist aprepitant that had been FDA approved since 2003.<sup>3-5</sup> ASCO added combinations of anthracyclines and cyclophosphamide to this high-risk category in 2011 and urged providers to also provide prophylactic NK-1 receptor antagonists to these patients.<sup>5</sup>

In parallel with its most recent antiemetic practice guidelines, ASCO launched the Quality Oncology Practice Initiative (QOPI) program in 2010. The purpose of the program is to promote practice improvement and increase the effectiveness of cancer

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**TABLE** Incidence of all grades and grade 3/4 chemotherapy-related nausea and vomiting

Reference	Regimen, dose+dosage, n	Disease	Any grade, %	Grade 3/4, %
Coiffier <sup>11</sup> Lenz <sup>12</sup>	CHOP 197 160	Lymphoma	44-48	6-8
Coiffier <sup>11</sup> Lenz <sup>12</sup>	R-CHO 202 62	Lymphoma	42-45	4
Valle <sup>13</sup>	Cis, 25 mg/m <sup>2</sup> 2 wk on, 1 wk off 204	Biliary	NR	9
Gupta <sup>14</sup>	Cis, 30 mg/m <sup>2</sup> weekly 264	H+N	NR	3.4
Rose <sup>15</sup>	Cis, 40 mg/m <sup>2</sup> weekly 253	Cervical	60	12
Hagan <sup>16</sup>	Cis, 20 mg/m <sup>2</sup> days 1-3 35	Bladder	NR	11

CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; Cis, cisplatin; H+N, head and neck, NR, not reported; R-CHO, CHOP + rituximab

care in addition to increasing accountability among practitioners.<sup>6</sup> Since its inception, more than 250 academic and community-based practices in the United States have completed the process and earned QOPI certification.<sup>7</sup> During the spring 2012 QOPI cycle, a QOPI metric specifically addressed the use of aprepitant or fosaprepitant prophylaxis with “high emetic risk chemotherapy” (Symptom 28), signaling its importance to the provision of quality cancer care.<sup>8</sup> Also in 2013, the ASCO Choosing Wisely campaign encouraged health care practitioners to be judicious with costly antiemetics to improve the cost effectiveness of cancer care. In the discussion, emphasis is placed on the additional cost and toxicity of these agents. Providers are encouraged to limit their use to circumstances in which chemotherapy with “high potential ... for severe and/or persistent nausea and vomiting” is used.<sup>9</sup>

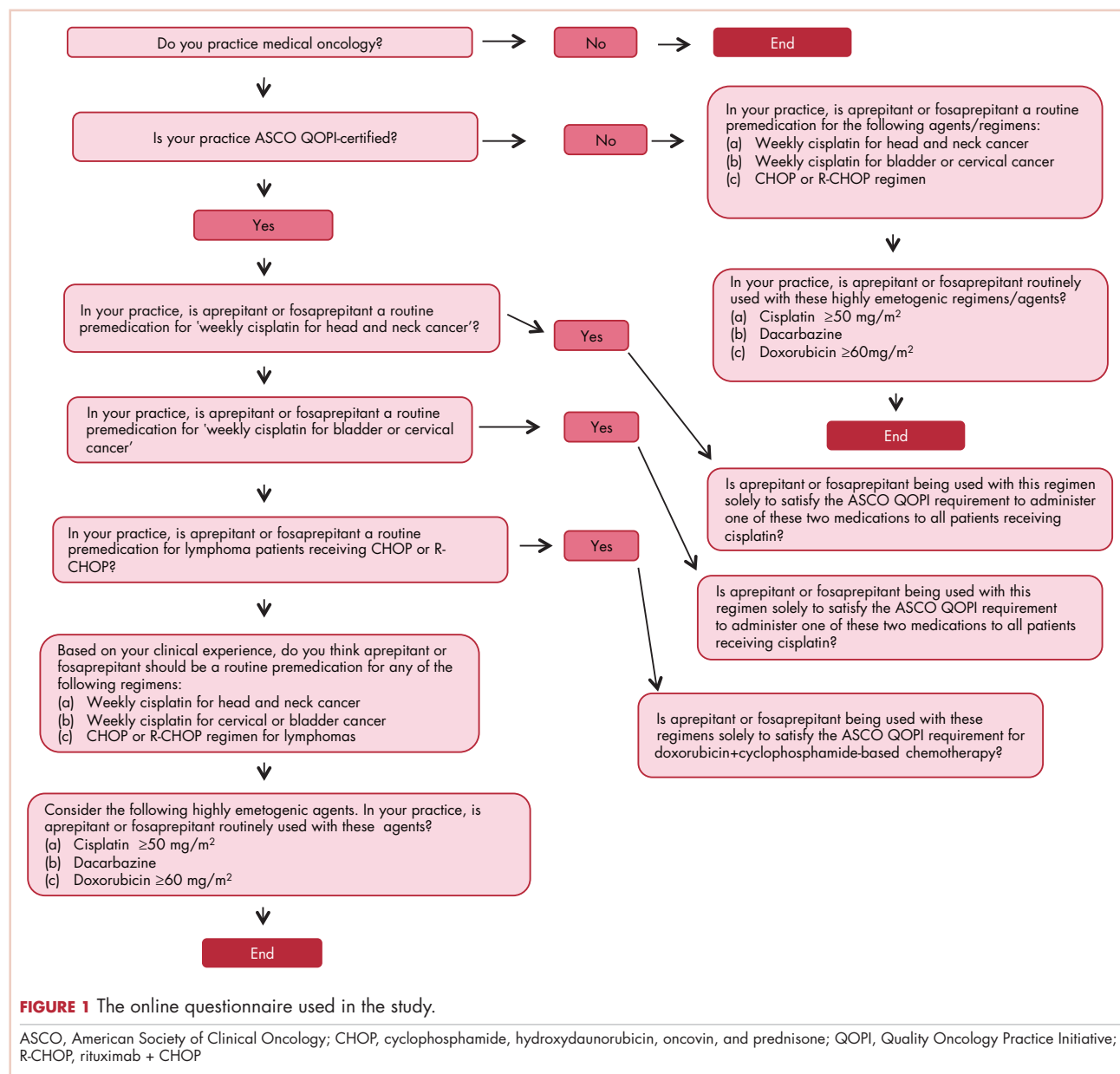
Aprepitant and fosaprepitant, are oral and intravenous NK-1 receptor antagonists, respectively. Both are moderate inhibitors of CYP3A4 and interact with commonly used medications metabolized through the CYP3A4 pathway, such as apixaban and diltiazem. In addition, prescribers must be cognizant of known interactions with corticosteroids, some anthracyclines, and tyrosine kinase inhibitors, which are frequently used in chemotherapy regimens.<sup>10</sup> Although the toxicity of these drugs as single agents is difficult to assess, fatigue, constipation, and weakness are attributed to their use.<sup>10</sup> Finally, the addition of these agents to prevent nausea and vomiting increases health care costs. The average wholesale price for a 3-day course of aprepitant is \$597.81; a single dose of fosaprepitant is \$308.35.<sup>10</sup> If these agents

are used pre-emptively with all cycles, the additional cost of treatment can soar to thousands of dollars.

We reviewed the primary literature to better understand the emetogenic risk of regimens that contain cisplatin or a combination of doxorubicin and cyclophosphamide. The total incidence (all grades) of nausea and vomiting ranged from 42%-72%, whereas the incidence of grade 3/4 nausea was 3.4%-12% (Table).<sup>11-16</sup> The only study to report on prophylactic antiemetics was one in which cisplatin 30 mg/m<sup>2</sup> was used in patients with head and neck cancer.<sup>14</sup> The patients received intravenous ondansetron 16 mg and dexamethasone 16 mg 30 minutes before chemotherapy. Based on these data, we questioned whether the widespread use of NK-1 receptor antagonists is clinically justified given the additional cost, toxicity, and drug interactions. We hypothesized that the prescribing patterns of oncologists are heavily influenced by the current ASCO and QOPI guidelines. We surmised that practitioners are using these agents to obtain QOPI certification, a mark of quality, rather than based on their clinical judgment. To answer this research question, we performed an online, survey-based assessment.

## Methods

We designed and administered an anonymous, 12-question, online survey to better understand the prescribing habits of medical oncologists as they pertain to NK-1 receptor antagonists (Figure 1). Survey responses were in a dichotomous Yes/No format. For questions pertaining to NK-1 receptor antagonist use with chemotherapy regimens, respondents

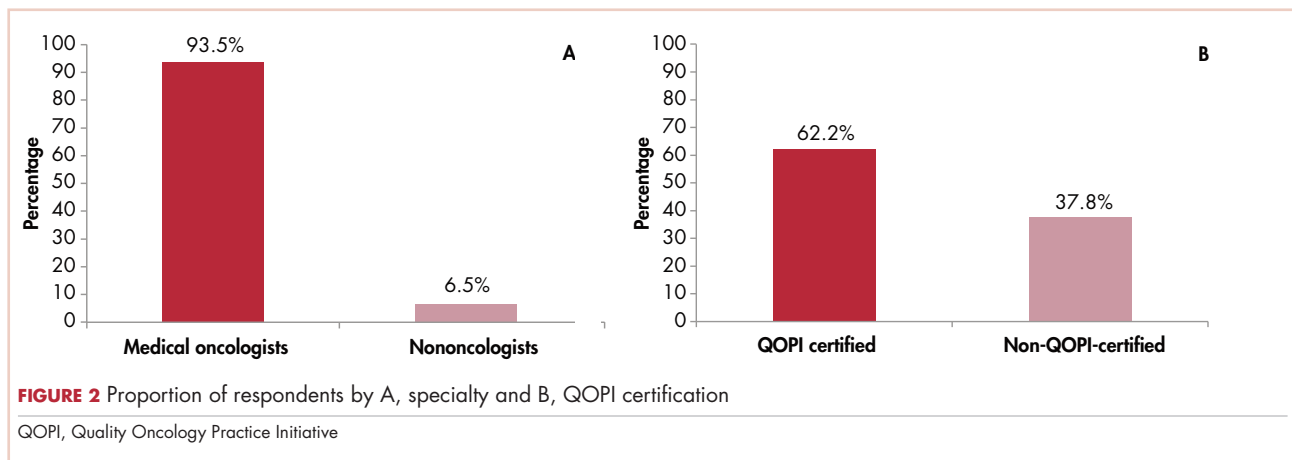


were permitted to answer Not Applicable if they did not prescribe that regimen in their practice. The survey was sent to academic and community-based medical oncologists in northern California, Arizona, Minnesota, North Dakota, and South Dakota without respect to QOPI certification. A total of 650 practitioners were polled.

For the purposes of this study, and because of the Hesketh classification, we refer to cisplatin doses of  $<50$  mg/m<sup>2</sup> and a cyclophosphamide-plus-anthracycline combination with doxorubicin dose  $\leq 50$  mg/m<sup>2</sup> as moderately emetogenic.

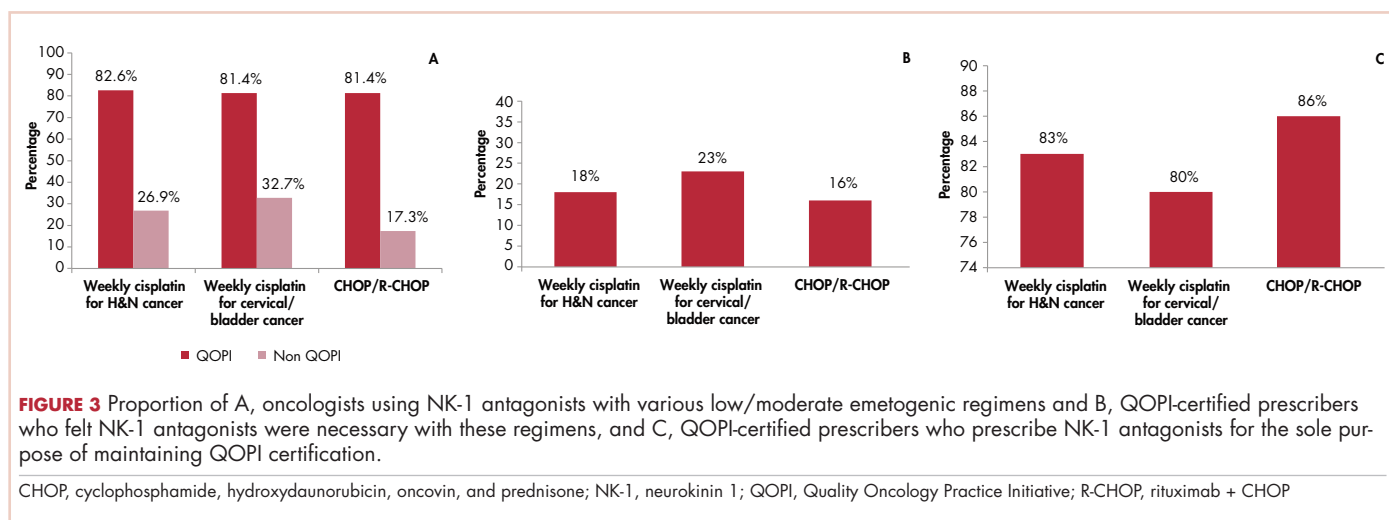
In our survey, health care providers from QOPI-certified practices were asked whether they prescribed prophylactic NK-1 receptor antagonists for moderately emetogenic reg-

imens, such as weekly cisplatin (for head and neck cancer, or bladder and cervical cancers) and when cyclophosphamide is used in combination with an anthracycline, as in cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) without rituximab or with rituximab (R-CHOP). Those who answered affirmatively were asked whether their motivation was compliance with the ASCO guidelines and subsequent QOPI certification. Next, we asked these providers whether, based on their clinical experience and judgment, they thought that NK-1 receptor antagonists *should* be used in the setting of weekly cisplatin or with CHOP/R-CHOP. Finally, practitioners were asked whether they routinely prescribed these agents with the highly emetogenic chemotherapy regimens: cisplatin  $\geq 50$  mg/m<sup>2</sup>, doxo-



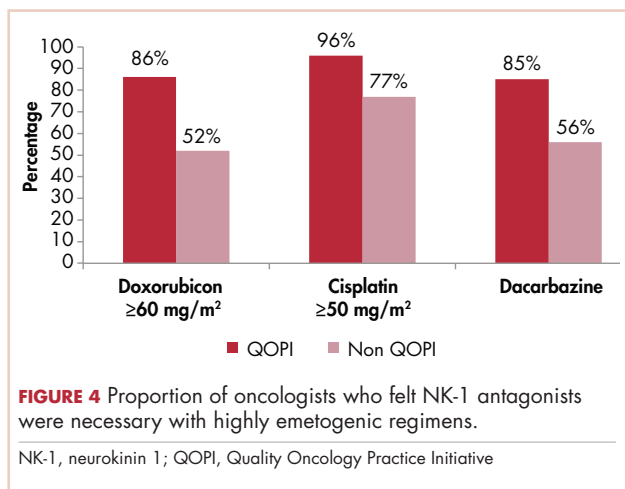
**FIGURE 2** Proportion of respondents by A, specialty and B, QOPI certification

QOPI, Quality Oncology Practice Initiative



**FIGURE 3** Proportion of A, oncologists using NK-1 antagonists with various low/moderate emetogenic regimens and B, QOPI-certified prescribers who felt NK-1 antagonists were necessary with these regimens, and C, QOPI-certified prescribers who prescribe NK-1 antagonists for the sole purpose of maintaining QOPI certification.

CHOP, cyclophosphamide, hydroxydaunorubicin, oncovin, and prednisone; NK-1, neurokinin 1; QOPI, Quality Oncology Practice Initiative; R-CHOP, rituximab + CHOP



**FIGURE 4** Proportion of oncologists who felt NK-1 antagonists were necessary with highly emetogenic regimens.

NK-1, neurokinin 1; QOPI, Quality Oncology Practice Initiative

rubin  $\geq 60$  mg/m<sup>2</sup>, or dacarbazine. Doxorubicin, at dose of 60 mg/m<sup>2</sup>, is frequently used in the treatment of young women with breast cancer who are at high-risk for chemotherapy-related nausea and vomiting.<sup>17-19</sup>

Noncertified practitioners were presented with an abbreviated form of the survey, which contained identical ques-

tions that asked about NK-1 receptor antagonist use in the same clinical settings.

The data from the surveys were analyzed in aggregate using likelihood ratio chi-square tests. *P* values of  $< .05$  are reported as significant. Descriptive statistics are used to describe the differences between groups.

## Results

In all, there were 155 unique survey responses for a response rate of 23.8%. Most of the respondents identified themselves as medical oncologists (145/155, 93.5%, Figure 2) and went on to complete the survey. Nearly two-thirds (62.2%) of the respondents were from QOPI-certified oncology practices (89/143, Figure 2).

Providers from QOPI-certified practices were significantly more likely to prescribe NK-1 receptor antagonists in conjunction with moderately emetogenic regimens than were providers from non-QOPI practices. In the setting of weekly cisplatin for head and neck cancer, 82.6% of practitioners from QOPI-certified practices used these agents, compared with 26.9% from noncertified practices ( $P < .001$ ). Similar patterns were observed with weekly

cisplatin for cervical and bladder cancer (81.4% vs 32.7%,  $P < .001$ ) and with CHOP/R-CHOP (81.4% vs 17.3%,  $P < .001$ , Figure 3).

When asked about their rationale for using these agents, a majority of the certified respondents replied that they used them to maintain their QOPI certification (80%-85.7%, Figure 3). When asked if aprepitant and fosaprepitant were clinically indicated in these settings based on their clinical judgment and/or personal experience, only a minority of certified respondents replied affirmatively (17.3%-32.7%, Figure 3). Weekly cisplatin for the treatment of bladder or cervical cancer received the strongest endorsement from the QOPI-certified physicians, whereas CHOP/R-CHOP was the regimen they felt least compelled to use.

Finally, we inquired about the use of these agents in the setting of highly emetogenic chemotherapy regimens, in which the use of NK-1 receptor antagonists is indicated because of their high emetic potential. In all cases, providers from QOPI-certified practices were more likely to prescribe these agents than were providers from non-QOPI practices (85.0%-96.0% vs 51.9%-76.9%, respectively;  $P < .001$ ; Figure 4).

## Discussion

Our data demonstrate that providers from QOPI-certified practices were significantly more likely to prescribe NK-1 receptor antagonists than were those in noncertified practices. Of note is that the certified physicians reported that satisfying the ASCO-QOPI requirements was their primary motivation for offering the agents. This may be due, at least in part, to the relatively low incidences of grade 3/4 nausea and vomiting associated with the moderately emetogenic chemotherapy regimens discussed here.

Several limitations should be considered when inter-

preting these results. First, as with any survey-based assessment, practitioners with strong opinions may be more likely to participate than those with neutral opinions. This response bias may detract from the generalizability of our findings to the general population of medical oncologists. Second, although our conclusions were statistically significant, our dataset included only 155 responses (out of some 13,000 practicing medical oncologists nationally). Consequently, the views presented may not accurately reflect the sentiments of the national medical oncology community. Third, the brevity of our survey prevented us from collecting meaningful information about demographics and clinical judgment (academic or private, clinical scenarios when clinicians feel these agents are necessary, and so on).

Despite those limitations, we hope that our work will stimulate a productive discussion on the usage of these agents in clinical practice. In this era of emerging targeted therapies, many of which are capable of altering the natural history of a disease, our patients are on track to receive more lines of chemotherapy than ever before. The excitement for these agents, however, has been tempered by public outcry over their price. As Kantarjian and his colleagues have noted, the price of treatment has climbed logarithmically since 2000. Before then, a year of antineoplastic therapy cost less than \$10,000, but by 2012, the 12 or 13 new drugs approved that year carried an annual price tag of more than \$100,000 per patient receiving them.<sup>20</sup> Patients who fail these agents eventually receive second- and third-line therapies, each with an additional layer of cost, resulting in burgeoning health care expenditures that are not sustainable. We as providers of cancer care must endeavor to temper quality of care with cost-conscious health care. And above all, we cannot and should not ignore our clinical judgment.

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