Developing Drugs for Prevention of Chemotherapy-Induced Nausea and Vomiting: Draft Guidance from the FDA

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ABSTRACT

The administration of preventative therapy for chemotherapy-induced nausea and vomiting (CINV) is an essential component of the treatment plan for many patients with cancer. In May 2021, the FDA issued a draft guidance for industry to facilitate the clinical development of drugs for the prevention of CINV in adults. FDA guidance has a vital role in the regulatory dialogue between the Agency and external stakeholders. Sharing the FDA's current recommended approach can expedite drug development and ultimately the availability of safe and effective therapies to patients in need. In addition, guidance documents may be leveraged to facilitate communication between regulatory agencies, the academic community, patient advocacy groups, and the pharmaceutical industry. The draft guidance for industry *Chemotherapy-Induced Nausea and Vomiting: Developing Drugs for Prevention* (May 2021) outlines the FDA's current recommendations regarding clinical development programs for drugs for the prevention of CINV and the required attributes of patients for enrollment, aspects of trial design, and efficacy assessments. This article provides an overview of the recommendations contained in the draft guidance.

Introduction

According to patients undergoing chemotherapy for cancer, chemotherapy-induced nausea and vomiting (CINV) is the adverse effect of treatment that has the greatest impact on their quality of life (1). It has been estimated that 80% of patients receiving chemotherapy experience CINV (2). CINV can suppress appetite, compromise nutrition, and cause dehydration. If persistent, these sequelae can progress to metabolic derangements. Furthermore, inadequately controlled CINV may result in patient noncompliance with, or withdrawal from, antineoplastic therapy, thus directly affecting a patient's overall prognosis.

Because of the burden and possible implications of CINV, the administration of prophylactic therapy for CINV is considered standard of care for patients receiving chemotherapy with moderately or highly emetogenic agents. Adequate prevention of CINV typically requires a combination of drugs from several therapeutic classes, and multiple professional organizations, including the American Society for Clinical Oncology (ASCO; refs. 3, 4), have published recommendations for preventative treatment regimens according to the emetogenicity of the chemotherapeutic agents that are to be administered. Additional guidelines are available from the National Comprehensive Cancer Network (https://www.nccn.org/professionals/physician_gls/pdf/antiemesis.pdf), the Multinational Association for Supportive Care in Cancer (https://www.mascc.org/clinical-guidelines), and the European Society For Medical Oncology (https://www.esmo.org/guidelines/supportive-and-palliative-care/prevention-of-chemotherapy-and-radiotherapy-induced-nausea-and-vomiting).

The ASCO guidelines categorize chemotherapy regimens associated with a 90% or greater incidence of nausea and vomiting in the absence of antiemetic prophylaxis as highly emetogenic chemotherapy (HEC) and those associated with a 30% to 90% incidence as moderately emetogenic chemotherapy (MEC). These definitions of HEC and MEC should be used when designing drug development programs.

CINV is also classified according to the time of symptom onset relative to chemotherapy administration as occurring in the acute phase (onset 0 to ≤24 hours) or the delayed phase (onset >24 to ≤120 hours). The overall phase of CINV is defined as the presence of symptoms from 0 to 120 hours following chemotherapy administration. Although the overall phase (onset within 0 to 120 hours) is commonly referred to in clinical practice, for clinical trials intended to support the demonstration of substantial evidence of effectiveness, dedicated independent assessments of investigational products in the acute and delayed phases are preferred over an assessment in the overall phase to provide information to inform optimal use. See *Efficacy Assessments*.

In May 2021, the FDA issued a draft guidance for industry to facilitate the clinical development of drugs for the prevention of CINV in adults (5). Unless otherwise specified, references to drugs in this article encompass both small-molecule drugs and therapeutic biological products. The draft guidance outlines the FDA's current recommendations regarding clinical trials for drugs for the prevention of CINV and the recommended attributes of patients for enrollment, aspects of trial design, and efficacy assessments. The draft guidance does not address the development of drugs for the treatment of CINV in patients who are already experiencing symptoms as a result of chemotherapy.

Drug Development Program Considerations

Trial population

To support an indication for the prevention of acute, delayed, or acute-and-delayed nausea and vomiting associated with HEC, patients should receive cisplatin or one of the other chemotherapeutics classified as HEC by the ASCO guidelines.

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Of note, although the ASCO reclassified anthracycline/cyclophosphamide (AC) chemotherapies from MEC to HEC in 2011, AC chemotherapy has been demonstrated to be less emetogenic than other agents classified as HEC (e.g., cisplatin). In addition, the recommended standard-of-care preventative regimens for CINV described in the ASCO guidelines for the prevention of CINV differ between adults treated with cisplatin and other highly emetogenic single agents and adults who received AC chemotherapy (3, 4). Therefore, data obtained solely from AC chemotherapy-based trials are not considered adequate to demonstrate substantial evidence of effectiveness in patients receiving other HEC regimens. To support a demonstration of efficacy for patients receiving non-AC HEC, development programs that include patients who received AC chemotherapy should include multiplicity-controlled analyses of the primary and ranked secondary endpoints limited to patients receiving non-AC HEC (according to the ASCO guidelines).

An indication for the prevention of CINV in patients receiving MEC may be supported by demonstration of substantial evidence of the drug's effectiveness in adequate and well-controlled trials involving patients receiving HEC and availability of sufficient data to support the safe use of the drug in patients receiving MEC. If an independent indication for the prevention of CINV in patients receiving MEC is being sought, the trial population(s) should receive chemotherapeutic agents classified as MEC by the ASCO guidelines.

Finally, patients with brain metastases should be included in early drug development trials to facilitate the collection of data to inform the development of eligibility criteria in later-phase trials. In cases where there is a strong rationale for exclusion, the rationale should be described in the trial protocol. For additional recommendations, see the guidance for industry, *Cancer Clinical Trial Eligibility Criteria: Brain Metastases* (July 2020; ref. 6).

Trial design

Patients should receive standard-of-care background antiemetic therapy in accordance with the ASCO guidelines. To facilitate interpretation of the trial's efficacy and safety results, these regimens should be standardized across all treatment arms. In addition, permitted rescue medications and their administration schedule should be standardized.

If the goal is to demonstrate the superiority of a given drug in addition to standard of care compared with standard of care alone, a randomized, double-blind, and placebo-controlled trial design is recommended.

If the goal is to demonstrate the non-inferiority or superiority of an agent to an approved therapy, a randomized, double-blind, active comparator trial design is recommended (7). Any such trial should include an active comparator arm [standard-of-care antiemetic prophylaxis (drugs from two to four classes as recommended by the ASCO)] and an investigational treatment arm, with the investigational treatment replacing the drug of the same class used in the comparator arm.

Efficacy Assessments and Statistical Considerations

Efficacy assessments

Clinical trials intended to support an indication of the prevention of CINV should use a primary efficacy endpoint of a *complete response*, defined as no vomiting and no use of rescue antiemetic medication; and a secondary endpoint of the *absence of nausea*, defined as no nausea and no use of rescue antiemetic medication, to establish efficacy for the prevention of CINV.

Demonstration of a significant treatment effect on the primary endpoint of a complete response (no vomiting and no use of rescue antiemetic medication) in the absence of a significant treatment effect on the secondary endpoint (no nausea and no use of rescue antiemetic medication) may not be sufficient to support an indication for prevention of the nausea component of the CINV indication.

Depending on the mechanism of action of the drug and expected timing of the primary effects of treatment, the period(s) for efficacy endpoint assessments should be prespecified as acute (0 to ≤24 hours), delayed (>24 to ≤120 hours), or acute and delayed phase(s).

A secondary endpoint of assessment of efficacy in the overall phase (onset within 0 to 120 hours) may be included; however, the overall phase should not be selected for primary efficacy assessments, as drugs are often found to be effective for either acute or delayed onset CINV, and this information is needed to inform optimal use in patients receiving various chemotherapy regimens.

To support the efficacy of a drug over repeated courses of chemotherapy, its efficacy should be demonstrated during at least four chemotherapy cycles.

Statistical considerations

The analyses of the primary endpoint (i.e., a binary endpoint defined as no vomiting and no use of rescue antiemetic medication) and secondary endpoint (i.e., a binary endpoint defined as no reported nausea and no use of rescue antiemetic medication) should evaluate the difference in the proportion of responders across treatment arms.

To enhance the precision of the evaluation of overall treatment effects, statistical analyses should adjust for baseline characteristics that may influence efficacy outcomes (e.g., younger age, female sex, history of morning sickness, history of no or low use of alcohol, history of previous chemotherapy, the presence of central nervous system lesions, and history of motion sickness), and subgroup analyses and evaluation of potential treatment interactions based on these factors should be considered.

Clinical outcome assessments

FDA input should be sought both as early as possible and at important milestones throughout the drug development process to help inform the selection or development of clinical outcome assessment (COA) instruments and COA-based endpoints that are appropriate for the context of use. The design of the instrument selected, including the specific response options in the questions included, should be informed by qualitative data from patients to demonstrate that the measurement strategy adequately captures patients' experiences of nausea.

In general, data should be collected regarding: (i) the severity of the patient's nausea at its worst during the recall period (e.g., using a verbal rating scale with response options such as *none, mild, moderate*, and *severe*), (ii) the frequency and/or duration of nausea, and (iii) the effect of nausea on the patient's daily living and functioning.

Patient-reported outcome instruments should capture assessments daily (e.g., using a recall period of the prior 24 hours) and assessments should be completed at the same time each day (e.g., in the evening before bedtime). The primary endpoint of a complete response (i.e., no vomiting and no use of rescue antiemetic medication) and the secondary endpoint of no nausea and no use of rescue antiemetic medication may be assessed using either the same or different instruments for each endpoint.

For additional recommendations, see the guidance for industry, Food and Drug Administration staff, and other stakeholders, *Patient-Focused Drug Development: Collecting Comprehensive and Representative Input* (June 2020; ref. 8). For general recommendations for patient-reported outcome assessments (as well as information relevant to other COAs) and the document to be provided to FDA for review, see the guidance for industry, *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* (December 2009; ref. 9).

Concluding Remarks

This guidance is intended to facilitate discussion and encourage the development of products for the prevention of CINV. It may be accessed on the FDA website at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/chemotherapy-induced-nausea-and-vomiting-developing-drugs-prevention-guidance-industry.

Authors' Disclosures

No disclosures were reported.

Disclaimer

The information in these materials is not a formal dissemination of information by the FDA and does not represent its position or policy on any matter.

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