



Reducing dexamethasone antiemetic prophylaxis during the COVID-19 pandemic: recommendations from Ontario, Canada

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Abstract

Purpose People with cancer face an elevated risk of infection and severe sequelae from COVID-19. Dexamethasone is commonly used for antiemetic prophylaxis with systemic therapy for cancer. However, dexamethasone is associated with increased risk of viral and respiratory infections, and causes lymphopenia, which is associated with worse outcomes during COVID-19 infections. Our purpose was to minimize dexamethasone exposure during antiemetic prophylaxis for systemic therapy for solid tumors during the COVID-19 pandemic, while maintaining control of nausea and emesis.

Methods We convened an expert panel to systematically review the literature and formulate consensus recommendations.

Results No studies considered the impact of dexamethasone-based antiemetic regimens on the risk and severity of COVID-19 infection. Expert consensus recommended modifications to the 2019 Cancer Care Ontario Antiemetic Recommendations.

Conclusion Clinicians should prescribe the minimally effective dose of dexamethasone for antiemetic prophylaxis. Single-day dexamethasone dosing is recommended over multi-day dosing for regimens with high emetogenic risk excluding high-dose cisplatin, preferably in combination with palonosetron, netupitant, and olanzapine. For regimens with low emetogenic risk, 5-HT₃ antagonists are recommended over dexamethasone.

Keywords COVID-19 · Antiemetic · Supportive care · Chemotherapy · Glucocorticoids

Introduction

The COVID-19 pandemic is growing exponentially, with over two million infections and 130,000 deaths worldwide as of April 15, 2020 [1]. Early evidence suggests that patients with cancer face an elevated risk for COVID-19 infection and a higher risk of adverse events after diagnosis [2–5], potentially because of nosocomial spread and suppressed immunity.

Several guidelines for pandemic era cancer care have been recently released [6–13]. These guidelines make prudent recommendations on optimizing the delivery of systemic therapy during the COVID-19 pandemic, including to:

1. Favor oral agents over intravenous agents when efficacy and toxicity profiles are similar [6, 7].
2. Deliver oral agents and supportive medications directly to the homes of patients, rather than have them picked up in person at the pharmacy [6].
3. Favor regimens with less frequent over more frequent IV dosing when efficacy and toxicity profiles are similar [6].
4. Favor intermittent treatment strategies and breaks over continuous strategies when efficacy and toxicity profiles are similar and patients are stable [6, 7].
5. Defer the use of medications whose primary role is to reduce the risk of long-term complications such as bone disease, where appropriate [6].
6. Favor neoadjuvant over adjuvant treatment strategies when efficacy and toxicity profiles are similar, to facilitate

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the delay of surgical dates and increase the availabilities of hospital beds and ventilators [7].

7. Use GCSF for primary prophylaxis in high-risk regimens [7].

We convened an expert panel to formulate recommendations on modifications to antiemetic prophylaxis during the COVID-19 pandemic to protect cancer patients. We recognize the limitations of such a document, given the rapidly evolving environment and paucity of data.

Methods

An expert panel was convened to review potential modifications to antiemetic prophylaxis for systemic therapy for solid tumors during the COVID-19 pandemic. The panel included medical oncologists, infectious disease physicians, and pharmacists from the Princess Margaret Cancer Centre and Cancer Care Ontario.

We conducted a systematic literature search to evaluate all current literature on COVID-19 and antiemetics, including peer-reviewed and published studies in PubMed (<https://www.ncbi.nlm.nih.gov/pubmed/>, accessed April 15, 2020) and pre-prints in medRxiv (<https://www.medrxiv.org/>, accessed April 15, 2020). We searched (“COVID” or “SARS-COV-2” or “Coronavirus”) and “Cancer” and (“antiemetics” or “nausea” or “vomiting” or “emesis”) in PubMed on April 15, 2020 and combinations of each of these terms in medRxiv. We also reviewed the websites of provincial (BC Cancer [9], Cancer Care Ontario [11]) and international (ESMO [8], American Society of Clinical Oncology [7], National Comprehensive Cancer Network [10]) oncology organizations.

We developed recommendations based on the literature review and expert consensus. Recommendations were developed through virtual meetings and email correspondence until full consensus was achieved.

Given the paucity of data on COVID-19 and antiemetic prophylaxis, recommendations were based on expert opinion and the modification of recent evidence-based guidelines developed before the COVID-19 pandemic, in particular the Cancer Care Ontario guidelines for Antiemetics [14].

Recommendations: how should COVID-19 impact antiemetic prophylaxis?

Recommendation 1

Prescribe the minimal effective dose of glucocorticoids (Table 1).

Recommendation 2

If nausea or vomiting occurs despite the recommended regimens, increase or add non-glucocorticoid agents such as an NK₁ agent or olanzapine, before increasing the glucocorticoid dose.

Recommendation 3

If no nausea or vomiting occurs with prior cycles, consider further reductions in dexamethasone.

Evidence summary

No studies identified through the systematic review assessed the impact of antiemetic dosing and the risk or severity of COVID-19 in cancer patients.

Our recommendations focus on minimizing glucocorticoid use for oncology patients because data support a dose-dependent association between glucocorticoids and viral and respiratory infections [15–17]. Glucocorticoids cause immunosuppression through multiple complex mechanisms, in particular by altering gene transcription of pro-inflammatory genes like interleukins and nuclear factor-kappa-B. Glucocorticoids also deplete T and B cells essential for the immune response to viruses [18].

In COVID-19, lymphopenia is common and associates with more severe disease [19], suggesting the importance of lymphocytes in the immunological response. Currently, guidelines recommend against using glucocorticoids to treat respiratory failure associated with COVID-19 in the absence of acute respiratory distress syndrome or patient-specific indications like concomitant chronic obstructive pulmonary disease exacerbation [20]. This recommendation is based on a signal of harm when using glucocorticoids to treat other viral infections, including influenza [21] and SARS [22].

To determine glucocorticoid dosing for chemotherapy during the COVID-19 pandemic, we started with the 2019 Antiemetic Recommendations for Chemotherapy-Induced Nausea and Vomiting from Cancer Care Ontario (CCO) [14]. The CCO guidelines are based on the latest evidence and are generally consistent with those of the American Society for Clinical Oncology [23] (ASCO) and the Multinational Association of Supportive Care in Cancer and European Society of Medical Oncology [24] (MASCC/ESMO) guidelines. CCO provides a classification of emetogenic risk for anticancer regimens (<https://www.cancercareontario.ca/en/AntiemeticGuideline>, accessed March 27, 2020).

We modified the 2019 CCO guidelines for highly emetogenic chemotherapy to include single-day dosing of dexamethasone for all regimens except high-dose cisplatin based on meta-analyses that show similar efficacy between

Table 1 Changes to the Cancer Care Ontario antiemetic guidelines during the COVID-19 Pandemic. Changes from the general CCO guidelines are emphasized in bold

| Regimen | General CCO Guidelines [14] | COVID-19 modifications | |
|--|--|--|---|
| Single-day IV | | | |
| Highly emetogenic chemotherapy | <u>Steroid</u> <i>Day 1</i> Dexamethasone 12 mg PO or 10 mg IV <i>Day 2 to 3–4</i> Dexamethasone 8 mg PO or 10 mg IV. Note only day 1 is required for anthracycline and cyclophosphamide regimens for breast cancer. | If highly emetogenic, excluding high-dose cisplatin: <u>Steroid</u> <i>Day 1</i> Dexamethasone 12 mg PO or IV No dexamethasone after day 1. | |
| | <u>5-HT₃</u> <i>Day 1</i> Granisetron 2 mg PO or 1 mg IV OR Ondansetron 8 mg PO BID or 8 mg IV OR Palonosetron 0.25 mg IV or 0.5 mg PO | <u>5-HT₃</u> <i>Day 1</i> NEPA (netupitant 300 mg + palonosetron 0.5 mg) (preferred with single-day dexamethasone as NEPA in combination with netupitant) OR Granisetron 2 mg PO or 1 mg IV OR Ondansetron 8 mg PO BID or 8 mg IV | |
| | <u>NK₁</u> <i>Day 1</i> Aprepitant 125 mg PO OR Fosaprepitant 150 mg IV OR NEPA (netupitant 300 mg + palonosetron 0.5 mg) PO <i>Day 2–3</i> Aprepitant 80 mg PO daily (days 2–3) if started on Day 1 | <u>NK₁</u> <i>Day 1</i> NEPA (netupitant 300 mg + palonosetron 0.5 mg) (preferred with single-day dexamethasone as NEPA in combination with netupitant) OR Aprepitant 125 mg PO OR Fosaprepitant 150 mg IV <i>Day 2–3</i> Aprepitant 80 mg PO daily (days 2–3) if started on Day 1 | |
| | <u>Thiobenzodiazepine</u> <i>Day 1</i> Olanzapine 5 mg PO daily <i>Day 2–4</i> Olanzapine 5 mg PO daily or 2.5 mg BID | <u>Thiobenzodiazepine</u> <i>Day 1</i> Olanzapine 5 mg PO daily <i>Day 2–4</i> Olanzapine 5 mg PO daily or 2.5 mg BID | |
| | <u>Steroid</u> <i>Day 1</i> Dexamethasone 8 mg PO or 10 mg IV <i>Note, for taxanes, prefer 20 mg IV × 1 30 min before for hypersensitivity or infusion reactions</i> | Unchanged. | |
| | <u>5-HT₃</u> <i>Day 1</i> Granisetron 2 mg PO or 1 mg IV OR Ondansetron 8 mg PO BID or 8 mg IV OR Palonosetron 0.25 mg IV or 0.5 mg PO | | |
| | <u>Steroid</u> Dexamethasone 8 mg PO or 10 mg IV | <u>5-HT₃</u> <i>Day 1</i> Granisetron 2 mg PO or 1 mg IV OR Ondansetron 8 mg PO BID or 8 mg IV OR Palonosetron 0.25 mg IV or 0.5 mg PO | |
| | No antiemetics recommended | Unchanged | |
| | Multiple-day IV | | |
| | Highly emetogenic chemotherapy | <u>Steroid</u> Dexamethasone 12 mg PO or 10 mg IV on day 1 and then 8 mg PO or 10 mg IV (up to two days after the last dose of therapy) | <u>Steroid</u> Dexamethasone 12 mg PO or 10 mg IV on the days of chemotherapy |
| <u>5-HT₃</u> Granisetron 2 mg PO or 1 mg IV OR Ondansetron 8 mg PO BID or 8 mg IV | | <u>5-HT₃</u> Granisetron 2 mg PO or 1 mg IV OR Ondansetron 8 mg PO BID or 8 mg IV | |
| <u>NK₁</u> Aprepitant 125 mg PO on Day 1 then 80 mg PO daily (up to 2 days after last dose of chemotherapy) | | <u>NK₁</u> Aprepitant 125 mg PO on Day 1 then 80 mg PO daily (up to 2 days after last dose of chemotherapy) | |
| <u>Thiobenzodiazepine</u> Olanzapine 5 mg PO and then 5 mg PO daily or 2.5 mg PO BID (up to 2 days after last dose of chemotherapy) | | <u>Thiobenzodiazepine</u> Olanzapine 5 mg PO and then 5 mg PO daily or 2.5 mg PO BID (up to 2 days after last dose of chemotherapy) | |
| Moderately emetogenic chemotherapy | <u>Steroid</u> <i>Day 1</i> Dexamethasone 8 mg PO or 10 mg IV <u>5-HT₃</u> | Unchanged | |

Table 1 (continued)

| Regimen | General CCO Guidelines [14] | COVID-19 modifications |
|--|--|------------------------|
| | <i>Day 1</i> Granisetron 2 mg PO or 1 mg IV OR Ondansetron 8 mg PO BID or 8 mg IV | |
| Oral chemotherapy | | |
| Moderate to high | <u>5-HT₃</u> Granisetron 2 mg PO or ondansetron 8 mg PO BID | Unchanged |
| Minimal to low | No routine prophylaxis; PRN recommended | Unchanged |
| Breakthrough nausea and vomiting | Prefer olanzapine 2.5 mg PO BID PRN, max 10 mg daily if given in combination with prophylaxis | Unchanged |

single- versus multiple-day dosing of dexamethasone [25, 26]. The 2019 CCO guidelines recommended single-day dosing only for anthracycline and cyclophosphamide combinations, where the evidence is strongest. However, we have extended single-day dosing to all highly emetogenic chemotherapies given the potential risks of dexamethasone during the COVID-19 pandemic and because the meta-analyses included trials that showed similar efficacy for single-day dexamethasone dosing across a variety of moderately and highly emetogenic regimens, including carboplatin, oxaliplatin, paclitaxel, and irinotecan [27–29]. Single-day dexamethasone in these trials was investigated in combination with NEPA, a combination of palonosetron (a longer-acting 5-HT₃ agent) and netupitant (an NK₁ agent). Therefore, we have recommended NEPA as the preferred agent in combination with single-day dexamethasone. We have included other 5-HT₃ and NK₁ agents as acceptable alternatives to NEPA because concomitant use of an NK₁ agent prolongs the half-life of dexamethasone [30] and we recommend standing and as needed olanzapine, which is effective for any breakthrough nausea and vomiting that occurs [31]. We excluded high-dose cisplatin from the recommendation because a trial showed inferior outcomes with single- versus multiple-day dosing [32].

Further reduction of dexamethasone dosing below 12 mg on day 1 may increase nausea and vomiting, which could lead to hospitalizations and increased risk of COVID-19. For example, a randomized controlled double-blinded randomized trial compared 4, 8, 12, or 20 mg of dexamethasone IV combined with ondansetron during cisplatin [33]. Rates of nausea with 8 versus 12 mg of dexamethasone were 61.0 and 66.9%, respectively, while rates of vomiting were 69.1% and 78.5%, respectively.

We modified the 2019 CCO guidelines for low emetogenic risk regimens to substitute a 5-HT₃ agent rather than dexamethasone, consistent with the ASCO [23] and MASCC/ESMO [24] guidelines, which recommended either 4–8 mg of dexamethasone or a 5-HT₃ agent based on consensus among the expert panel. There are no randomized controlled

studies or meta-analysis of antiemetic prophylaxis among low-emetogenic risk regimens.

These recommendations should be individualized for each patient, considering patient-specific risk factors or prediction models for emesis [34]. Prior nausea and vomiting with chemotherapy [35], female sex, and younger age are associated with a higher risk of emesis [34, 36]. Prescribers should also consider the potential toxicities and interactions of the agents substituted for dexamethasone.

Discussion

Cancer patients face an elevated risk of infection, serious complications, and death from COVID-19. Our Recommendations aim to protect cancer patients from the harms of COVID-19 by reducing their exposure to dexamethasone. Given the rapid advances in COVID-19 research, we will update these recommendations continuously as new information becomes available.

Author contributions All authors contributed to the study conception and design. Robert Grant performed the literature review and wrote the first draft of the manuscript. All authors commented on subsequent versions of the manuscript and read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest Monika Krzyzanowska reports receiving funding to the University Health Network from Eisai and Exelixis; and receiving personal fees from Eisai outside the submitted work

The remaining authors declare that they have no conflicts of interest.

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