Journal of Oncological Sciences 3 (2017) 99–101

Contents lists available at ScienceDirect

Journal of Oncological Sciences

journal homepage: https://www.elsevier.com/locate/jons

An overview of the latest ASCO recommendations about antiemetic prophylaxis for treatment-related nausea and vomiting

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ARTICLE INFO

Article history:
Received 1 September 2017
Received in revised form
6 September 2017
Accepted 7 September 2017
Available online 15 September 2017

Keywords:
Palliative care
Nausea
Vomiting
NK1 antagonists
Olanzapine
5HT3 antagonist antiemetic prophylaxis

ABSTRACT

Nausea and vomiting (N&V) are among the most feared symptoms of cancer treatment. Since treatment-related N&V is predictable up to some extent, a systematic approach is recommended for prevention. Recently, ASCO has updated and released its' guideline for the prevention of treatment-related N&V. This paper is aimed to summarise the key changes and recommendations of ASCO for practicing medical or radiation oncologists treating adult cancer patients.

Palliation of symptoms related to disease or treatment itself has been perceived as a sacred privilege and responsibility of physicians since ancient times. A cancer patient may experience many different types of symptoms, like pain, nausea & vomiting (N&V), dyspnea, etc., which should be palliated appropriately. Needless to say, N&V is among the most feared symptoms of cancer patients. Cancer treatment related N&V is somewhat predictable and should be approached in a systematic way. The Macmillan dictionary defines "*to palliate*" as "to reduce the pain or other bad effects of an illness without curing it completely."[1] However in case of treatment related N&V, contemporary aim is complete prevention.

After the discovery of ondansetron, the first potent and selective 5-HT3 receptor antagonist, in 1984 and FDA approval of this agent in 1991, many single or combinations of drugs have been studied to prevent treatment related N&V in cancer patients. And in time different societies, like MASCC, ESMO and ASCO, have endorsed guidelines regarding the management of treatment related N&V. Several after others recently, an update of antiemetics guideline has been released online by ASCO on 31 July 2017.[2]

In this update, a panel of experts in the field conducted a systematic review of literature which focused only on randomised controlled trials (RCTs) and systematic reviews between November 1, 2009 and June 1, 2016. The review process yielded 41 publications (35 RCTs and 6 meta-analyses), majority about prevention of chemotherapy-related N&V, and less publications about radiation-induced N&V and for paediatric patients found.

Regarding the prevention of treatment-induced N&V, specific recommendations made for each emetogenic risk stratum (Table 1).

High-emetic risk, single-day chemo: Efficacy of addition of olanzapine (10 mg/day, po, D1-4), which is an antipsychotic drug that blocks multiple neurotransmitters in central nervous system, to standard of care (SOC; NK1 antagonist + dexamethasone 12 mg on D1/8 mg D2-4 + 5HT3 antagonist) was tested in patients treated with high-emetogenic risk chemotherapy.[3] The NCI funded study showed the superiority of olanzapine to SOC, at the cost of an increased sedation on day 2, in primary and secondary end points, defined as no nausea during the overall assessment period (0–120 h) and complete response (no emetic episodes and no rescue medication), respectively. In the light of these data, ASCO panel revealed the new SOC antiemetic regimen that should be used for high-emetogenic risk drugs as a 4-drug combination (NK1 antagonist + 5HT3 antagonist + dexamethasone + olanzapine). To note, for antracycline and cyclophosphamide regimen dexa is

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Peer review under responsibility of Turkish Society of Medical Oncology.

http://dx.doi.org/10.1016/j.jons.2017.09.001

Table 1
Summary of recommendations for antiemetic prophylaxis according to emetogenic-risk category of single-day i.v. chemotherapy.

Antiemetic prophylaxis for single-day chemotherapy according to emetogenic risk

High-emetogenic	cisplatin or other HE-chemo	Olanzapine (continue D2-4)	NK1 antagonist	5HT3 antagonist	dexamethasone (continue D2-4)
	antracycline + cyclophosphamide	Olanzapine (continue D2-4)	NK1 antagonist	5HT3 antagonist	dexamethasone (D1 only)
Moderate emetogenic	Carboplatin ≥ AUC4	-	NK1 antagonist	5HT3 antagonist	dexamethasone
	no agents with delayed emesis risk	-	-	5HT3 antagonist	dexamethasone (D1 only)
	agents may cause delayed emesis *	-	-	5HT3 antagonist	dexamethasone (may be offered D2-3 also)
Low emetogenic		-	-	single dose 5HT3 antagonist or	single dose dexamethasone 8 mg
Minimal emetogenic	no routine antiemetic prophylaxis				

*Drugs such as cyclophosphamide, oxaliplatin or doxorubicin.

recommended only for the first day, if a 4-drug antiemetic combo will be used.

In this update, another NK1 antagonist, rolapitant which was formerly approved by FDA in 2015, listed among the options that could be used in the treatment of CINV. Also, non-inferiority of subcutaneous extended release granisetron to i.v. palonosetron and superiority to ondansetron were shown in different trials.

Moderate-emetic risk, single-day chemo: Recommendations regarding moderate-emetogenic regimens could be reviewed in 3 parts. First, patients receiving carboplatin with a dose AUC $\geq$4 are accepted at the higher end in terms of emesis risk in this category. Studies of both rolapitant and aprepitant showed superior emesis prophylaxis in these patients with regard to 5HT3 + dexa combination. Therefore current update recommends NK1 antagonists plus 5HT3 and dexa for patients who will receive carboplatin AUC $\geq$4. Second, for the majority of moderate-emetogenic regimens a combination of 5HT3 + dexa on D1 only would be enough. However, if the patient will receive an agent that is known to cause delayed emesis (like cyclophosphamide, oxaliplatin or doxorubicin) dexa may be offered for D2-3, also. Third, different form the previous version of this guideline, palonosetron is no longer the agent of choice for moderate-emetogenic risk drugs owing to lack of convincing data, thus any 5HT3 antagonist is acceptable for this risk group.

Low-emetic risk, single-day chemo: Since the quality of evidence about antiemetic prophylaxis is low for this stratum, the guideline proposed single 5HT3 antagonist or single dose 8 mg dexamethasone with an informal consensus and moderate strength of evidence.

Minimal-emetic risk, single-day chemo: As previous, these patients should not be offered routine antiemetic prophylaxis, unless foreseen such a need by the treating physician.

Administering the most effective antiemetic prophylaxis that is appropriate according to emetogenic risk category is seen as a principle of practice. Lorazepam is an adjunctive drug but not recommended as a single agent whereas diphenhydramine is no longer accepted as an adjunctive drug for emesis prophylaxis. Trials with cannabinoids are old and no comparison with contemporary antiemetics is found. As of today evidence remains insufficient for a recommendation regarding medical marijuana use or complementary/alternative therapies (such as ginger, acupuncture, acupressure etc.) for the prevention of treatment related N&V in patients with cancer. Addition of NK1 antagonists to 5HT3 + dexa combination is recommended because of positive findings from 2 different aprepitant studies in patients undergoing high-dose chemo for stem cell transplantation. In patients receiving multi-day chemo, the most active prophylaxis appropriate for emetogenic risk category plus continuing antiemetics 2 more days after completion of chemo is recommended. For breakthrough emesis, always consider to re-evaluate emetic risk, disease status, concurrent illnesses, and medications first, which may be reasons of emesis other than treatment itself. Later, think of olanzapine if not

previously administered, if patient received olanzapine then consider to add an agent with a different mechanism of action (such as NK1 antagonist, lorazepam, alprazolam, dopamine receptor antagonist, etc.). Behavioural therapy with systematic desensitisation is the unchanged recommended approach for patients with anticipatory emesis.

There are also recommendations about the antiemetic approach for radiation therapy (RT) in this update. For high (risk > 90%, total body irradiation) and moderate risk (30–90%, craniopsinal, upper abdomen RT) radiation therapies, prophylactic approach with 5HT3 plus dexamethasone is recommended. Whereas for low (risk 10–30%, brain, head&neck, thorax, pelvis) or minimal risk (<10%, extremity, breast) RT, a rescue strategy is recommended primarily with 5HT3, dexamethasone or dopamine antagonist. The emetic risk of anti-neoplastic agent should guide the antiemetic prophylaxis in patients receiving chemoradiotherapy unless the risk related with RT is higher.

The last topic that ASCO guide touched is the health disparities issue regarding the availability of antiemetic drugs in different populations within US. Research have told us that under treatment in terms of antiemetic prophylaxis for some patient populations in US is obvious due to several reasons. For Turkey, to the best of my knowledge, we do not have such data proving that some patients are under treated due to lack of drugs or a reluctance to prescribe. But the fact is we have had experienced transient drug shortages because of various reasons and thankfully authorities have tried to solve those problems in a relatively short period of time.

This antiemetic guideline clearly recommends olanzapine as an additive to previous SOC treatment for high-emetogenic chemo and NK1 antagonists for patients receiving carboplatin AUC $\geq$4. A relevant question that arise in minds is when a community practicing medical oncologist in Turkey will be able to prescribe these agents to her/his patients in appropriate clinical settings? I do believe that authorities responsible for drug approval and reimbursement in Turkey must be proactive in this regards, especially if the issue is related with palliation of symptoms or quality of life improvement. Other questions that might be interesting for clinical researchers are; does is worth it to test olanzapine in moderate-emetogenic chemo? or which is better for low-emetogenic chemo, dexamethasone or 5HT3 antagonists?

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