Neurotoxicity of Anti-Cancer Drugs & Neuroprotection by New Antiemetic Molecules

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ABSTRACT

Neurotoxicity of anti-cancer drugs as manifested by nausea and vomiting remains among the most feared side effects of chemotherapy for cancer patients. Such neurotoxic effects often compromise the availability of treating molecules to the site of action. These undesired side effects greatly destroy the quality of life of cancer patients with very high impact such as start of neuropathies, cardiopathies, alopecia and other diverse effects. Significant progress has been made during the last decade in developing more effective and better tolerated measures to minimize chemotherapy-induced nausea and vomiting. The selective 5-hydroxytryptamine receptor antagonists were first introduced in the 1990s for the treatment of chemotherapy induced nausea and vomiting (CINV) . The pre-treatment with 5-HT antagonists among with anti-cancer drugs permitted in more effective and better tolerated management of CINV. Despite recent progress, however, a large number of patients still develop CINV, particularly during the 2-5 day period called as delayed emesis following chemotherapy. Some clinicians underestimate the true magnitude of this problem as it was shown that there was a consistent overestimation by caregivers of the level of emetic control being achieved for the patients suffering from severe neurotoxic effects leading to CINV. Thus, there remains a compelling need to identify effective new neuroprotective drugs or treatments such as hematopoitic-stem cell transplantations for reducing CINV and neuropathologic degradation.

Before going into detail about the mechanism of action of anti-emetic agents, we shall try to differentiate pharmacological as well as pathophysiological aspects of anti-cancer drug induced emesis. What is the site of action of anti-cancer drugs and how anti-emetic molecules provide neuroprotection? The role of enterochromaffin cells, vagotomy and 5-HT concentration in gastrointestinal tract as well as in the central nervous system especially in the area postrema, are they all directly or indirectly implicated in the control of neurotoxic response?. Effects of anti-cancer drugs are very severe and effective on skin, alopecia, loss of hair, hypoplastic anaemia and finally nausea and vomiting. Back ground of anticancer drug induced emesis leads to stimulation of enterochromaffin cells in the gastrointestinal tract and may liberate free radicals and increase the concentration of 5-HT in GI tract as well as brain regions. The different patterns and types of emesis linked to cisplatin toxicity causing organ damage and dysfunction of GI tract during acute and chronic treatments are elaborated in response to 5-HT3 antagonists along with steroids. Other aniemetic agents tested were phenothiazine, prochlroperazine and chloropromazine etc are dopamine antagonists. Benzodiazepine, steroids such as dexamethasone, methylprednisolone and prednisolone were also tested for their efficacy to counterbalance neurotoxic effects of anti-cancer drugs. However, 5-HT3 antagonists were found to be more efficient as neuroprotective molecules

The present conference will also review different class of antiemetic drugs that have received approval for therapeutic administration. The first generation of 5-HT3 receptor antagonists representing ondansetron, dolasetron, granisetron and tropisetron, form the cornerstone of the antiemetic therapy for moderately to highly emetogenic chemotherapy. The efficacy and safety of these new drugs

has been repeatedly demonstrated in controlled clinical trials especially for the prevention of acute emesis often observed during the first 24 hours following cancer chemotherapy.

Higher vomiting center in the central nervous system was localized to be area postrema. It was also observed that 5-HT concentrations in the hippocampus, the medulla oblongata and hypothalamus increased significantly 72 hours after a single dose of cisplatin. The administration of ondansetron, a selective 5-HT3 receptor antagonist reduced significantly the incidence of cisplatin-induced emesis in dose dependent ratio. It was found that bioavailability of orally administered ondansetron is approximately 60 % of intraperitoneally administration. IP and PO administrations efficacy for ondansetrone to slow down anticancer drug induced toxicity was found 76 % IV vs 83% PO. The ultrastructural studies by electron microscope localized 5-HT stored in large electron-dense granules which move towards the base of EC cells and released from the basal surface during emesis. Other physiological approaches such as vagotomy significantly inhibited cisplatin induced emesis by 80%. Combination of ondansetron and vagotomy significantly inhibits cisplatin-induced increase in 5-HT in the area postrema but not in the ileum. Such observations provide evidence that cytoxic drugs induce emesis mainly through their action on the gastrointestinal tract. Nafamostat, a protease inhibitor, inhibits methotrexate induced 5-HT release from the ileum 72 hours after administration of this anticancer drug. COX-2 inhibitors and dexamethasone on cisplatin induced emesis and release of 5-HT from ileum were also studied.

CONCLUSIONS:

More studies are necessary comparing 5-HT3 anatagonists alone or combined with steroids or protease inhibitors or COX-2 inhibitors to achieve a better antiemetic response during delayed emesis and a marked reduction in neurotoxic effects.

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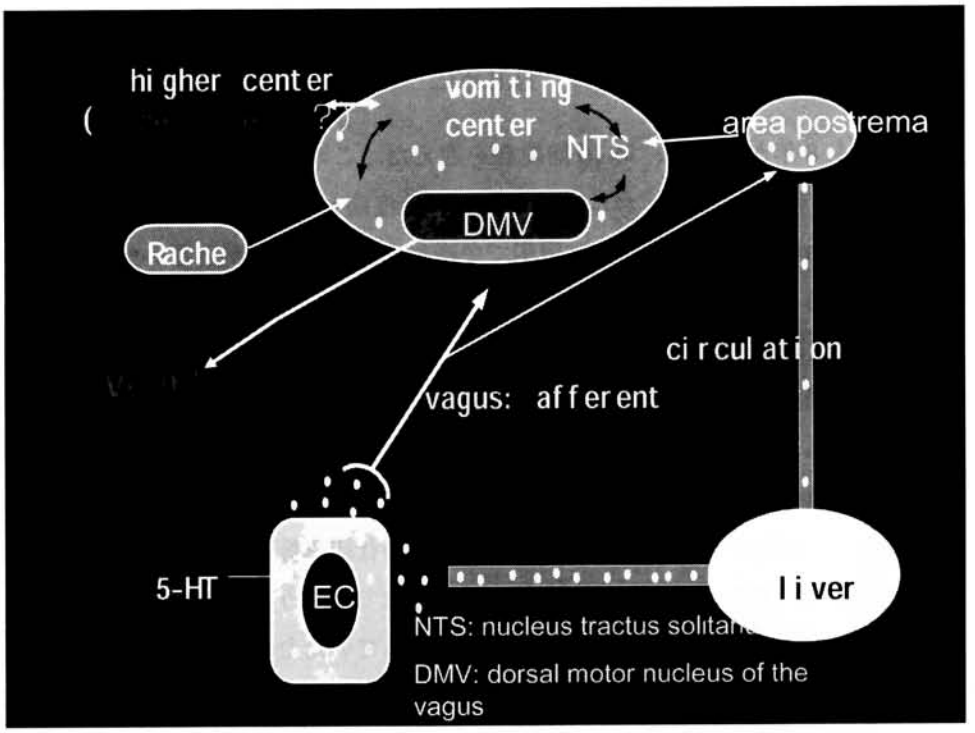

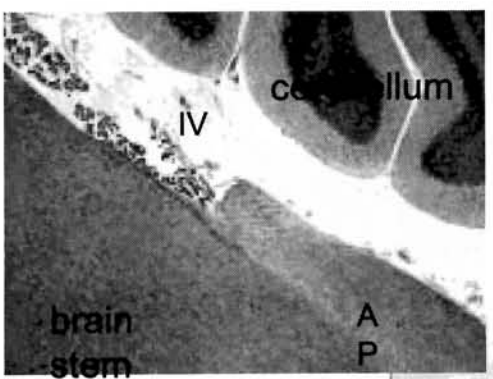

AP:area postrema

= chemoreceptor trigger zone

IV: IVth vetriculus

NTS: nucleus tractus solitarius