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The Oncology Pharmacy Newsletter is publication dedicated to providing useful information for the staff treating patients who come to the Oncology Outpatient Pavilion.

Questions and requests for topics are welcome.

References available upon request.

Management of Docetaxel – Induced Fluid Retention

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Docetaxel is an antimitotic agent used in several cancers such as breast cancer, non-small cell lung cancer, gastric cancer, castrate-resistant prostate cancer, and head and neck cancer.[1] The medication works by promoting the stabilization of microtubules, thereby inhibiting DNA, RNA, and protein synthesis.[2] Although docetaxel has been shown to be beneficial in a variety of different cancers, it is associated with several black- boxed warnings.[1] Fluid retention is one of those and it often leads to discontinuation of therapy.[1] Therefore, appropriate management of this adverse effect is a key component when administering docetaxel.

Docetaxel-induced fluid retention can manifest as peripheral edema, pleural effusion, or ascites.[1,3] It commonly starts in the lower extremities and may become generalized, with a median weight gain of 2 kg.[1] Patients often complain of difficulty walking and stiffness in the joints.[3] The phenomenon occurs in a dose related manner. At doses of 60 mg/m^2, 75 mg/m^2, and 100 mg/m^2, the percentage of patients with fluid retention is 26%, 38%, and 46% respectively.[1] This effect of docetaxel is usually not observed right away and typically occurs after 3-5 cycles of chemotherapy.[3] It is slowly reversible after discontinuation of therapy and takes a median of 16 weeks to resolve.[1]

The pathophysiology of docetaxel-induced fluid retention is not completely understood. It is hypothesized to be due to capillary leak syndrome.[5] Similarly, capillary leak syndrome doesn't have a clear etiology but is thought to be due to inflammation and endothelial damage.[5] This leads to increased permeability, which causes increased amounts of intravascular fluid to go into the interstitial space.[5] Docetaxel plays a role in facilitating this pathway by being a potent inhibitor of endothelial cell function, leading to the damage and inflammation observed.[4]

Corticosteroids are often used to prevent docetaxel-induced fluid retention because they decrease inflammation and more specifically, reverse capillary permeability.[6] A study completed in 1997 first examined the use of corticosteroids in this setting. In the study, patients receiving docetaxel were randomized to receive either 40 mg methylprednisolone on days -1, 0, 1, 7, 8, and 9 of each treatment cycle or nothing.[7] The results showed a statistically significant higher dose of docetaxel to onset of fluid retention and lower rate of fluid retention in patients receiving methylprednisolone.[7] A statistically significant longer time to onset of fluid retention also occurred in the group of patients receiving methylprednisolone.[7] Overall, the study proved that corticosteroids can help delay fluid retention experienced with docetaxel, which allows optimization of therapy.

A follow up study was done in the same year, 1997, with the aim of finding the optimal pre-treatment regimen to prevent docetaxel-induced fluid retention. Patients were either randomized to no premedication, dexamethasone 8 mg PO twice daily for 5 days, dexamethasone 8 mg PO twice daily for 3 days, or dexamethasone 8 mg PO twice daily for 3 days with diosmine, a vascular protectant agent.[8] The results of the study displayed no significant difference between the 5-day and 3-day regimen in regards

to the occurrence and onset of fluid retention. The study also concluded that diosmine did not add significant benefit.[8] Therefore because of fewer side effects associated with a shorter duration of corticosteroid therapy, the 3-day regimen became favored and led to the package insert regimen of docetaxel. The package insert states that patients should be pre-medicated with "corticosteroids such as dexamethasone 16 mg per day for 3 days starting 1 day prior to administration of docetaxel".[1] For patients being treated for prostate cancer that receive prednisone concurrently with docetaxel, 8mg of dexamethasone should be given at 12 hours, 3 hours, and 1 hour before administration.[1]

For the future, researchers have begun to look at single dose corticosteroids, specifically dexamethasone 20 mg IV prior to docetaxel administration, to combat patient adherence and side effect issues.[9] In a single center, retrospective study completed in 2010, breast, lung, and head and neck cancer patients receiving docetaxel demonstrated a lower incidence of fluid retention (12.2%), with a single IV 20-mg dose of dexamethasone compared with the manufacturer package insert's incidence of 64.4% with the 3-day regimen.[9] A large enough trial with evenly dispersed baseline characteristics has not been established to confidently warrant use of this premedication strategy yet. However, several institutions have adopted this strategy in breast cancer patients to minimize the adverse effects of the 3-day regimen.[11]

In conclusion, it is important for healthcare providers to counsel the patient on the importance of adhering to their docetaxel pre-treatment regimen. Docetaxel administration has the potential to be delayed if patients forget to take their corticosteroid the day before treatment. Additional antiemetic dexamethasone is not required on the days dexamethasone is given for fluid retention.[10] Patients should be counseled on the side effects of dexamethasone, such as insomnia, nausea, hyperglycemia, etc.[6] It is also important to note that patients aren't required to take dexamethasone if they have had a bad experience with it in the past. However, substitution with other corticosteroids should aim to be equivalent to the total package insert dose of dexamethasone. If patients still complain of fluid retention despite proper pre-treatment, diuretics can be used as needed.[1]

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