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(REVIEW ARTICLE)

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Gemcitabine: Association with Thrombocytosis

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Abstract

Gemcitabine is a pyrimidine antimetabolite that affects DNA synthesis in the S-phase of the cell cycle. It is effective against cancers such as ovarian carcinoma, non-small cell lung cancer, and pancreatic cancer. However it causes significant side effects like myelosuppression, which leads to thrombocytopenia in about 71% of patients, prompting discontinuation of therapy. Even though thrombocytopenia is common, some patients experience thrombocytosis during Gemcitabine therapy, especially in the second and third cycles, possibly due to a rebound effect. Thrombocytosis is usually asymptomatic and occasionally leads to venous thrombosis, but its clinical significance is uncertain because of conflicting studies. Further research is required to understand the physiology behind thrombocytosis in Gemcitabine-treated patients. Fluctuations between thrombocytosis and thrombocytopenia need to be closely monitored. Management for Gemcitabine-induced thrombocytosis can be improved if more comprehensive studies are undertaken to explore the role of thrombocytosis in cardiovascular events.

Keywords: Gemcitabine; Thrombocytosis; Thrombocytopenia; Chemotherapy-induced thrombocytosis; Gemcitabine-induced myelosuppresion;

1. Introduction

Gemcitabine is a potent cytostatic drug from the pyrimidine antimetabolite group. It is a phase-specific drug that acts on S-phase of the cell cycle causing DNA synthesis disorders, ultimately leading to cell death. Major indications for Gemcitabine treatment include non-small cell lung cancer, ovarian carcinoma, breast cancer, urinary bladder cancer, inoperable pancreatic cancer, some sarcomas, cutaneous and peripheral T-cell lymphomas and some relapses of Hodgkin's lymphoma. [1,2] Gemcitabine is usually given as monotherapy or along with cisplatin. The major side effects of Gemcitabine include myelosuppression, particularly neutropenia and thrombocytopenia, flu-like syndrome, skin rash, radiation recall dermatitis, fever, balding, nausea, shank edema, dyspnea and drowsiness. [1,2] Vascular side effects and the prothrombotic potential of Gemcitabine are thrombotic microangiopathy, venous thromboembolism, acute arterial events such as vasculitis and digital ischemia, systemic capillary leak syndrome and reversible posterior leukoencephalopathy. [2,3]

2. Thrombocyte fluctuations

Thrombocytopenia is a common side effect in chemotherapy-induced toxicity. Myelosuppression caused by Gemcitabine leads to exhaustion of the bone marrow causing pancytopenia. Thrombocytopenia caused by Gemcitabine has been reported to be 71%. [4] Thrombocytopenia is common in patients treated with Gemcitabine that they often have to discontinue it because of hematologic toxicity and a reduction in platelet count below 100*10^9/L. [1]

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Contrary to this, thrombocytosis is a rare occurrence. It is only seen with certain chemotherapy drugs such as gemcitabine, vinca alkaloids, and irinotecan. Thrombocytosis with Gemcitabine chemotherapy alone or with cisplatin/carboplatin was found to be 49% and 46%. [4] A study found that the incidence of thrombocytosis with Gemcitabine treatment might be underestimated. They found that out of 60 patients treated with Gemcitabine at their clinic in the last two years, around a dozen of them were found to have thrombocytosis. [1]

One study looked at the detailed time course for platelet fluctuation in a patient being treated for bladder cancer with neoadjuvant therapy of Gemcitabine and cisplatin. After an initial response of thrombocytopenia for the first cycle of treatment, temporary episodes of thrombocytosis were seen at 36 days and 34 days after the 2nd and 3rd cycles, respectively. This was followed by myelosuppression and thrombocytopenia at the 3rd and 4th doses. [4] A similar observation was seen with patients being treated for pancreatic cancer with Gemcitabine. The number of thrombocytes was the highest during the 2nd and 3rd chemotherapy cycles. The levels normalized with completion or termination of treatment. [1] A rebound increase in platelet production after the thrombocyte nadir seen with the first cycle of treatment was found to be the mechanism behind this thrombocytosis. [1,4] Since the increase in thrombocytes is on the 1st day of the second cycle, the possibility of a rebound mechanism is reiterated. [1]

Implications of this thrombocytosis on venous thrombosis and the cardiovascular system were studied. Thrombocytosis, though mostly asymptomatic, rarely contributes to venous thrombosis when counts rise to 100*10^4/mm3.[5] Unlike chances of venous thrombosis for thrombocytosis that is recorded before chemotherapy treatment, thrombocytosis after Gemcitabine treatment is usually temporary and passes without complications.[1] On assessment of the occurrence of vascular events, specifically thromboembolism, within 6 weeks of Gemcitabine chemotherapy, no significance was found between patients with or without thrombocytosis.[6] However, contradictory to this, in a study by *Zecchina et. al*, chemotherapy-induced thrombophilia was studied in patients with lung cancer, a temporal relationship between thrombocytosis and the clinical onset of thrombotic events was suggested. Following treatment cycles with Gemcitabine and cisplatin, all 4 cases of thrombotic events that occurred were within 10 days of the second treatment cycle during which thrombocytosis was seen to occur. [7]

3. Future direction

The amount of material that is now available emphasizes the need for more investigation on the pathophysiological pathways causing thrombocytosis in gemcitabine-treated individuals. There needs to be a strong focus on the necessity of close platelet monitoring because of the abrupt transition from thrombocytosis to thrombocytopenia in gemcitabine-based chemotherapy. Thrombocytosis could play an important role in cardiovascular events of venous thrombosis post chemotherapy but very few studies have been undertaken to study these effects. Current studies have not taken into consideration the role played by functional disorders of thrombocytes, which are common in neoplasms and accentuated by chemotherapeutic drugs. Further research into this could help in guiding treatment for thrombocytosis induced by gemcitabine chemotherapy.

4. Conclusion

In conclusion, the occurrence of thrombocyte fluctuations on giving Gemcitabine as chemotherapy, requires monitoring. Further research into the mechanisms behind Gemcitabine-induced thrombocytosis and its potential cardiovascular risks would improve patient management and outcomes. Author should provide an appropriate conclusion to the article.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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