Exploring the link between Capecitabine and Mania in a case of Carcinoma Rectum

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Abstract

Underreporting of behavioral adverse effects is well known in patients undergoing chemotherapy for cancer. The behavioral Adverse Drug Reactions (ADR) could include delirium, insomnia, mood disturbances, or syndromal psychiatric diagnosis. Liaison with the psychiatry team is essential to address the evolution of new-onset behavioral symptoms and a high degree of sensitivity with good interdisciplinary coordination is expected during Pharmacovigilance of behavioral ADR. We report the emergence of Mania on Capecitabine and Oxaliplatin regimen in a case of carcinoma rectum. The possible role of the kynurenine pathway in the inflammatory cascade is hypothesized to be implicated in both cancer and mood disorders that require further research. A low dose of antipsychotics such as risperidone under supervised follow-up with psychiatrist is necessary to treat the organic mania. The report also highlights the importance of pharmacovigilance while reporting behavioral adverse effects in clinical practice and emphasizes the role of consultation-liaison psychiatry in the field of oncology.

Introduction:

The emergence of neuropsychiatric symptoms secondary to the use of antineoplastic agents is known but often underreported. Capecitabine and Oxaliplatin regimen is one of the standard chemotherapy regimens used in clinical practice for the treatment of carcinoma rectum. Capecitabine is a prodrug of 5-fluorouracil (5-FU) and is associated with several behavioral syndromes including encephalopathy, psychosis, and depression across heterogeneous subgroups. [1–7]. However, the emergence of syndromal mania is rarely reported with Capecitabine use in carcinoma rectum. The exact mechanism of development of syndromal manic symptoms due to capecitabine is not fully known but few hypotheses are linked with inflammatory cascade implicated in cancer and mood disorders[8,9]. Further regular adherence to pharmacovigilance guidelines may be overlooked especially in such cases where behavioral adverse effects are the only manifestations. We report the development of Euphoric mania after the initiation of the third cycle of chemotherapy with capecitabine in one of the patients.

Case report:

A 24-year-old, single, gentleman, with a diagnosis of Carcinoma (CA) Rectum, underwent surgery followed by chemoradiotherapy at our center. While he was on adjuvant chemotherapy of 3rd cycle, with a combination of capecitabine and oxaliplatin (CapOX regimen as per the schedule- Oxaliplatin was given intravenously as an inpatient dose calculated as body weight followed by T.Capecitabine to be taken orally by the patient twice daily for 14 days in each cycle). The oncology team started observing changes in his behavior after 3rdday of the 3rd cycle of chemotherapy. He started having awake nights with a duration of sleep up to three hours per night and overfamiliarity with strangers. Despite resuming his routine work, he was found to be excessively involved in cycling, physical exercise, and studying which wasn't his usual self. He started believing in various businesses investment while working at the grocery shop and would not be productive with customers due to excessive involvement in the tedious detailing of the transactions. During this week he

was found to be overgrooming and expressing increased attraction towards female friends than his usual self. These behavioral changes resulted in frequent reminding by family members and eventually stopped him from attending the shop. Considering changes in his usual self and insistence by the family, he discontinued the oral capecitabine for 4 days this phenomenon was consistent with the self-dechallenge. By the end of 4^{th} day, the family found that he could sleep well at night and he appeared calmer. The patient also noticed that he could fall asleep easily (sleep latency reduced to 10-15 minutes than 45-60 minutes earlier) and could feel fresh the next morning. Barring his biological functions, even after 5 days of stopping the capecitabine, he was over cheerful and overtalkative.

Patient-reported to oncology team and capecitabine was rechallenged as a part of treatment regimen while advising brief inpatient care to note the progression of affective symptoms. After rechallenging with the capecitabine, over the next two days, his behavioral problems worsened and he was referred to the Consultation-Liaison Psychiatry (CLP) team. After a detailed evaluation, it was evident that the patient had no significant past history of any psychiatric illness. A family history of psychiatric illness was suggestive of mood disorder (Depressive illness) in the first-degree relative. On Mental Status Examination (MSE) the findings revealed increased psychomotor activity, elated mood, high distractibility, and subjective reporting of racing thoughts. The score on Young's Mania Rating Scale (YMRS) at the first visit was 18 points. All the routine investigations were within normal limits including MRI Brain. He was prescribed Tab. Risperidone 2mg H.S. and chemotherapy with capecitabine were resumed in liaison with the oncology team. While on capecitabine and risperidone, his manic symptoms started to resolve over a week. The risperidone was further increased to 3 mg and the patient's manic symptoms remitted within the next week as evidenced by the drop in the YMRS score from 18 to 6. The patient was discharged and followed up on outpatient care.

The patient was followed up on monthly basis and was found to have premorbid functioning with no psychopathology on MSE (YMRS score of 0). He completed the scheduled chemotherapy cycles under the cover of Tab. Risperidone which was subsequently reduced to 2mg at the end of one month. Both capecitabine and risperidone were continued together to prevent any recurrence of symptoms.

As per the institutional and international guidelines on pharmacovigilance, the rare adverse Drug Reaction (ADR) was reported to the ADR monitoring center in central India. The information was registered using vigiflow and vigibase software under the unique ID for the registered ADR as IN-IPC-300572210[10].

Discussion:

Manic symptoms were reported during the third cycle of chemotherapy. The emergence of manic symptoms in the later part of chemotherapy regimens is consistent with the findings published earlier on capecitabine challenge hypothesis[7,11]. It is also noteworthy to know that Capecitabine is a prodrug of 5 FU, therefore the cumulative adverse effects in the form of mania cannot be ruled out after two cycles of chemotherapy [11]. The gradual resolution of manic symptoms after discontinuation of Capecitabine by the patient supports the dechallenge hypothesis. Further, rechallenging with the capecitabine coincided with the re-emergence of manic symptoms that were effectively controlled within a week after starting risperidone alone. In addition, the absence of previous mood episodes, absence of symptoms of delirium or encephalopathy during chemotherapy were characteristic findings of our case that were different from the report published earlier [7]. The typical age of presentation of mania, presence of a family history of mood disorder favors the diagnosis of primary mania, however, absence of previous mood episode, the challenge-dechallenge-rechallenge hypothesis with capecitabine chemotherapy favors the capecitabine induced ADR in the form of mania. The score of six on the Naranjo Nomogram Adverse Drug Reaction Scale also implied the probable association of capecitabine and mania.

As capecitabine is the first-line treatment for the CA rectum, the CLP team advised to continue it under the cover of oral risperidone, a potent dopamine blocker, useful to alleviate acute manic symptoms as well as exhibiting additional tumor inhibitory activity a focus of future research[12,13]. Since behavioral symptoms can limit the compliance to medications, we recommend a careful analysis of the need for continuing the chemotherapy agent in liaison with the psychiatry team in such cases.

The exact cause of the evolution of affective symptoms while on a chemotherapy regimen is a less researched area. Involvement of the kynurenine system in the pathophysiology and clinical symptoms of both cancer and bipolar disorder is a possible hypothesis supported by the recent literature [8,9]. The role of Pro-inflammatory cytokines such as TNF-α and IFN-γ assist the degradation of tryptophan through activation of alternative kynurenine pathway that results in the formation of Quinolinic acid and its metabolites that may exert neurotoxic effects on the Central Nervous System (CNS)[9]. The same mechanism is also postulated to be the reason for the promotion of tumor growth in cancer patients,[8] which requires further research in cancer research. While the role of risperidone in blocking the dopaminergic and serotonergic receptors as well as TNF alpha requires further exploration in the context of this ADR[8]. Further, it is interesting to note that concurrent radiotherapy and initial two cycles of chemotherapy with capecitabine were not associated with behavioral disturbances against isolated chemotherapy cycles in the later period. The possible cumulative toxic effect of capecitabine is postulated hypothesis for such a late occurrence of ADR. An alternative explanation evolves from the weaning effect of radiotherapy-induced anti-tumor immune activation because of the healing tendency of a healthy tissue that results in the resolution of inflammation in the aftermath of radiation exposure[14]. Activation of the kynurenine pathway in mood disorders is governed by the acute as well as chronic shift in the anti and pro-inflammatory response of the immune system[15]. This mechanism could support the hypothesis of maintenance of normal behavior during radiotherapy due to the pro-inflammatory response of the immune system which can indirectly shift the balance towards the anti-inflammatory end during the aftermath of radiotherapy resulting in prominent mood symptoms via activation of the kynurenine pathway[16,17].

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