CASE REPORT
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Capecitabine-related death in triple negative breast cancer: a case report

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ABSTRACT

Triple-negative breast cancer (TNBC) is an immunohistochemical subtype of breast neoplasia characterized by the absence of hormonal receptor and HER2 expression. Capecitabine has been increasingly used in the treatment of TNBC patients who did not achieve a pathological complete response (pCR) after neoadjuvant therapy, showing favorable survival outcomes. Adverse effects related to capecitabine use are common, including gastrointestinal, hematologic, and dermatologic toxicity. However, the drug is generally well tolerated, and fatal outcomes related to treatment are infrequent. Due to its atypical nature, this study reports a death associated with therapy. In the case presented, the patient developed pancytopenia and febrile neutropenia (FN) 18 days after starting chemotherapy, progressing to alveolar, gastrointestinal, vaginal, and urethral hemorrhage, followed by hemodynamic instability, cardiopulmonary arrest, and death. Mortality occurring so early after capecitabine initiation may be linked to genetic alterations in certain individuals, such as dihydropyridine (DPD) deficiency. Genetic testing to identify DPD gene defects could allow for chemotherapy dose adjustments and reduce toxicity prevalence; however, such testing is not routinely performed. Further studies are needed to substantiate and assess the degree of benefit of this investigation before capecitabine chemotherapy, as well as the appropriate course of action based on the results. In these patients, FN prophylaxis with recombinant granulocyte colony-stimulating factors (G-CSFs) may also be considered, although it is primarily recommended for chemotherapeutic agents with a higher risk of myelotoxicity. Additional research is necessary regarding the actual application of capecitabine in TNBC cases to evaluate effectiveness, tolerability, and improve patient management.

KEYWORDS: breast neoplasms; triple negative breast neoplasms; capecitabine; drug toxicity.

INTRODUCTION

Breast cancer is the most common neoplasm in women and the most frequently diagnosed malignancy[1]. Among the intrinsic subtypes classified by immunohistochemistry, triple-negative breast cancer (TNBC) is characterized by the absence of hormone receptor and HER2 expression. It has an incidence of 15 to 20% and is generally associated with a poorer prognosis, accounting for 5% of breast cancer-related deaths annually[2].

The absence of all three receptors precludes the use of targeted therapy, making chemotherapy the current standard systemic treatment for this type of tumor. Various therapies have been investigated to improve pathological complete response (pCR) rates in TNBC and enhance patient prognosis. Among these, the immunotherapeutic agent pembrolizumab has been shown to increase disease-free survival (DFS)[2,3]. In this context, capecitabine has emerged as another alternative; it is an oral prodrug of 5-fluorouracil, primarily used in the treatment of metastatic breast cancer[4,5]. Recent studies have highlighted it[5-8] as a potential option for adjuvant therapy in TNBC patients, particularly those who did not achieve pCR following neoadjuvant treatment, demonstrating improved overall survival (OS) and DFS outcomes.

Fatal outcomes associated with capecitabine are rare, with mortality due to adverse effects occurring in approximately 1 to 3% of breast cancer patients[9]. Capecitabine has a relatively safe pharmacological profile and is generally well tolerated[10]. Given the rarity of such events, this study aimed to report and analyze a case of a patient with TNBC who received capecitabine as adjuvant therapy and subsequently experienced a therapy-related fatal outcome.

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CASE REPORT

A 44-year-old woman from the Baixo Amazonas region in Pará. G2PC2A0. Menopause occurred at 43 years of age. She used combined oral contraceptives (COCs) for seven years and received quarterly contraceptive injections for eight years. She smoked for 13 years, 1.3 pack/year, but quit 13 years ago. She denies any family history of cancer or other significant pathologies.

The patient was referred to the mastology outpatient clinic for evaluation of a nodule in the left breast. Breast ultrasound (BUS) revealed a hypoechoic, irregularly shaped, vascularized nodular lesion measuring 2×2.3×2.4 cm, located at the 12 o'clock position, 0.7 cm from the skin, and classified as BIRADS® 4. A biopsy of the left breast confirmed the neoplasm as a poorly differentiated, grade III invasive ductal carcinoma, associated with a comedo-type intraductal component. Immunohistochemical analysis showed the carcinoma to be negative for hormone receptors and HER2, confirming the triple-negative subtype. The tumor exhibited 90% Ki-67 expression. The initial clinical staging was T2N0M0.

Neoadjuvant chemotherapy was initiated, consisting of 4 sessions of carboplatin AUC 5 and paclitaxel 175 mg/m^2, followed by 4 sessions of doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2. During treatment, the patient experienced only mild toxicity, including nausea, asthenia, and headache. Subsequently, she underwent left quadrantectomy and sentinel lymph node biopsy, which led to left axillary lymphadenectomy. The residual tumor after chemotherapy measured 1.5 cm, and of the 20 lymph nodes removed, 3 demonstrated carcinomatous metastases with capsular leakage.

After adjuvant radiotherapy, the patient began oral therapy with capecitabine at a dose of 1,000 mg/m^2 twice daily for 14 days, administered in 8 cycles of 21 days each. Eighteen days after starting the first cycle, the patient developed severe diarrhea and diffuse abdominal pain, categorized as grade 3 by the Common Terminology Criteria for Adverse Events Version 5.0 (CTC-AE) classification of adverse effects of diarrhea and colitis, with more than 10 daily bowel movements[10], as well as vomiting and oral lesions consistent with moniliasis. The blood count revealed hemoglobin (Hb) 10.9 g/dL, leukocytes 210/mm^3 (neutrophils 83.58/mm^3), and platelets 29,000/mm^3, leading to a diagnosis of febrile neutropenia (FN) due to chemotherapy toxicity. The patient was admitted to the referral hospital, where empirical antibiotic therapy with cefepime, for antipseudomonal coverage, and ciprofloxacin, to broaden the spectrum of gastrointestinal bacterial coverage, was initiated. Fluconazole was also started due to oral moniliasis. A blood culture was performed three days after the initiation of antibiotics and yielded negative results. Platelet transfusions were administered to manage thrombocytopenia during hospitalization, along with filgrastim, a granulocyte colony-stimulating factor. No imaging or genetic tests for dihydropyridine dehydrogenase deficiency were conducted during this period. After 6 days of hospitalization, the blood count showed Hb 9.27 g/dL, leukocytes 122/mm^3 (neutrophils 8.18/mm^3), and platelets 2,000/mm^3. The patient experienced significant clinical deterioration, with alveolar, digestive, vaginal, and urethral hemorrhage, followed by hemodynamic instability, cardiorespiratory arrest, and death.

DISCUSSION

In patients with TNBC and residual disease following neoadjuvant chemotherapy, the role of capecitabine was recently established through the randomized phase III clinical trial CREATE-X[6]. In this study, 887 patients with HER2-negative breast cancer who did not achieve pCR after neoadjuvant therapy were randomized into either a control group or a capecitabine group (1,250 mg/m^2, orally, twice daily, on days 1–14 of each 3-week cycle, for a total of 8 cycles). This patient population was selected based on the association between failure to achieve pCR and poorer prognosis, including reduced survival outcomes. The study demonstrated five-year OS and DFS benefits, which, after subgroup analysis, were primarily observed in patients with TNBC (DFS 68.9% *vs.* 56.1%, HR 0.58, 95%CI 0.39–0.87; OS 78.8% *vs.* 70.3%, HR 0.52, 95%CI 0.30–0.90), who comprised approximately 30% of the study population. Capecitabine was well tolerated, with no fatal outcomes reported.

A meta-analysis by Li et al.[5] evaluated seven clinical trials involving patients with early-stage TNBC and found a significant increase in OS and DFS with the addition of adjuvant capecitabine to standard chemotherapy with anthracyclines and taxanes. Similarly, another meta-analysis by Li et al.[8] reported comparable results, demonstrating that adjuvant capecitabine is the most effective therapeutic strategy compared to other chemotherapy-based interventions.

Adverse effects associated with capecitabine use are common and include gastrointestinal, hematologic, and dermatologic toxicities[4,9,11]. According to a meta-analysis evaluating the safety profile of capecitabine in TNBC across 11 studies, the most frequently reported adverse effects were diarrhea, hand-foot syndrome, and leukopenia, which were generally tolerable[11]. Two studies assessed the tolerability of capecitabine in real-world clinical practice, following the recommendations of the CREATE-X trial. A retrospective analysis conducted in the United States involving 23 TNBC patients, with a mean dose of 1,871 mg/m^2/day, found that 47.8% of patients required dose reductions, 69.6% experienced dose interruptions, and 34.8% discontinued treatment early due to toxicity, primarily caused by hand-foot syndrome, gastrointestinal symptoms, and pain/fatigue[12]. Another multicenter observational study of 129 Caucasian patients reported better tolerability, with 10.4% of the general population discontinuing treatment due to toxicity. Hand-foot syndrome, diarrhea, and neutropenia each affected 1.85% of patients. The initial dose administered was 1,250 mg/m^2 twice daily for 14 days, every 21 days, across 6–8 cycles[13]. None of the studies reported fatal outcomes related to the drug.

Lower doses of capecitabine may reduce toxicity[9]; however, few studies have evaluated the efficacy of lower-dose regimens in TNBC patients. Wang et al.[7] investigated the use of adjuvant capecitabine at a reduced dose (650 mg/m^2, twice daily) but with a longer treatment duration (one year) in patients with early-stage TNBC. The study demonstrated an improvement in five-year DFS, although no significant impact on OS was observed. Among the 221 patients in the capecitabine group, 4.1% discontinued treatment due to unacceptable toxicity, primarily hand-foot syndrome. Additionally, leukopenia and diarrhea/abdominal pain were reported in 23.5 and 6.8% of patients, respectively.

Fatal outcomes so early in the use of capecitabine may be the result of genetic alterations in certain individuals. Dihydropyridine (DPD) deficiency is an important factor that increases the risk of toxicity to fluoropyridimine (FP) drugs, such as 5-fluorouracil and capecitabine. This deficiency is related to a genetic variation that increases the concentration of the drug in the body. Complete DPD deficiency is extremely rare, while between 3 and 5% of cancer patients may have partial deficiency. In patients with complete deficiency, the mortality rate is almost 100% in exposure to FP. On the other hand, although less fatal, partial deficiency may be responsible for 43 to 59% of cases of serious or life-threatening toxicity due to the substance[14].

In this sense, genetic testing to identify defects in the dihydropyridine dehydrogenase (DPYD) gene could indicate adjustments in the chemotherapy dose and reduce the prevalence of toxicity. However, studies in the United States show that this genetic screening is generally not indicated in oncology guidelines and is also not usually adopted by specialists. This is because there is still a lack of studies to indicate when, how and which genetic tests to apply, as well as information on how to interpret the tests and how to modify the dose according to their results[15].

The definition of FN includes an oral temperature exceeding 38.3°C or two consecutive readings above 38°C within two hours, along with an absolute neutrophil count below 500/μL or below 1,000/μL with a predicted decline within the next 48 hours in patients undergoing systemic chemotherapy. Clinical signs of sepsis may also be considered in the diagnosis of this condition[16]. FN is a serious complication that typically arises 7 to 10 days after the last chemotherapy dose and has a mortality rate that can exceed 50%[17]. Therefore, identifying the infectious focus through clinical evaluation or cultures, along with the prompt initiation of antibiotic therapy, is essential to improving patient prognosis and reducing mortality rates[18].

Recombinant granulocyte colony-stimulating factors (G-CSFs), such as filgrastim and pegfilgrastim (PFG), a recombinant G-CSF protein, can be used as prophylaxis for FN. Ideally, all patients undergoing chemotherapy with an FN risk greater than 20% should receive one of these prophylactic agents; however, this would entail significant costs. Therefore, their use is primarily recommended in therapies associated with substantial myelosuppression, such as those involving docetaxel (DCX) and doxorubicin[19]. Although myelotoxicity and FN are less common with capecitabine, prophylaxis with PFG may also be considered[20].

CONCLUSIONS

Capecitabine is an important therapeutic option for patients with TNBC. Currently, its primary indication is for patients with residual disease following neoadjuvant chemotherapy, demonstrating benefits in survival and mortality outcomes. The drug is generally well tolerated and has lower toxicity compared to other chemotherapeutic agents. However, careful monitoring of adverse effects is necessary, particularly given the recent expansion of its use in TNBC patients. Investigating DPD deficiency may be valuable in predicting severe toxicity and could be crucial for dose adjustments in higher-risk patients. Further studies are needed to determine the benefits of routine DPD deficiency screening before initiating capecitabine therapy, as well as to establish appropriate management strategies based on test results. FN remains a serious complication, for which prophylactic measures may also be considered in these patients. Additionally, further research is required to evaluate the real-world application of capecitabine in TNBC, assessing its effectiveness, tolerability, and optimal patient management.

AUTHORS' CONTRIBUTION

GMMVJ: writing – original draft, writing – review & editing. ACSES: writing – original draft, writing – review & editing. DSACC: project administration, supervision, writing – review & editing. JCS: validation, writing – review & editing.

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