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Severe Hypocalcemia due to Sacituzumab Govitecan in Highly Pretreated Triple Negative Breast Cancer Old Patient

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INTRODUCTION

Patients with metastatic Triple-Negative Breast Cancer (TNBC) have a poor prognosis [1]. Sacituzumab Govitecan (SG) is an antibody-drug conjugate that contains the irinotecan active metabolite, SN-38, linked to a humanized monoclonal antibody targeting trophoblast cell surface antigen [2], which is overexpressed in many solid tumors and approximately in 90% of TNBC [2,3]. S.G demonstrated in a basket design phase I/II study [4], promising activity in multiple cancer cohorts and in international, multicenter phase 3 ASCENT trial a significant improvement of S.G over single-agent chemotherapies (capecitabine, gemcitabine, vinorelbine, eribulin) with respect to overall response rate (35% *vs* 5%), progression free survival (median 5.6 *vs* 1.7 months; Hazard Ratio [HR], 0.41; $p < 0.001$) and overall survival (median 12.1 *vs* 6.7 months; HR 0.48; $p < 0.001$) in TNBC patients who had received at least two chemotherapy regimens for advanced disease [5]. Key SG Treatment-Related Adverse Events (TRAEs) of grade ≥ 3 included neutropenia and diarrhea, that are toxicities attributable to its cytotoxic payload, SN-38 an active metabolite of irinotecan. A recent published sub-analysis demonstrated that SG has a manageable safety profile even in patients $\geq$ 65 years [6]. However, limited data are available in elderly patients because in ASCENT trial only 49 pts were older than 65 and 8 pts were older than 75 years. In addition, no real-world experiences in elderly patients have been published. This case report tried to share what we learn about diarrhea and hypocalcemia due to S.G in a metastatic TNBC, highly pretreated older patient in order to recognize earlier and to manage severe adverse events optimizing S.G treatment.

Keywords: Breast cancer; Toxicity; Triple negative; Highly pretreated; Sacituzumab govitecan; Hypocalcemia; Diarrhea; Elderly patient

CASE PRESENTATION

A 63 years patient with a long history of thrombocytopenia (with recurrent superficial vein thrombosis in the leg) referred to our center in 2006 for a luminal A left breast cancer, treated with conservative treatment followed by radiotherapy and hormone therapy with aromatase inhibitor.

A contralateral quadrantectomy and axillary dissection was performed in 2019 due to a TNBC with pleomorphic lobular histology and high proliferative index (Ki67 40%), staged as pT3N3a. An adjuvant chemotherapy with anthracycline and taxane was given. Eleven months after adjuvant chemotherapy completion a breast and bone relapse were diagnosis. Biopsy of the breast nodule confirmed the relapse from the TNBC with histological characteristic of the primary tumor.

The patient received a first line treatment with oral metronomic chemotherapy [7-11] associated with Denosumab [12] as bone target agent and cholecalciferol plus calcium supplementation according to guideline [13]. After 11 months a subcutaneous huge spread of the disease was diagnosis; thus, she started as second line polychemotherapy with carboplatin plus gemcitabine [14], discontinuating denosumab. After 7 months from the second line beginning, a further subcutaneous progression was observed and Eribulin as a III line chemotherapy line was given [15] (Figure 1).

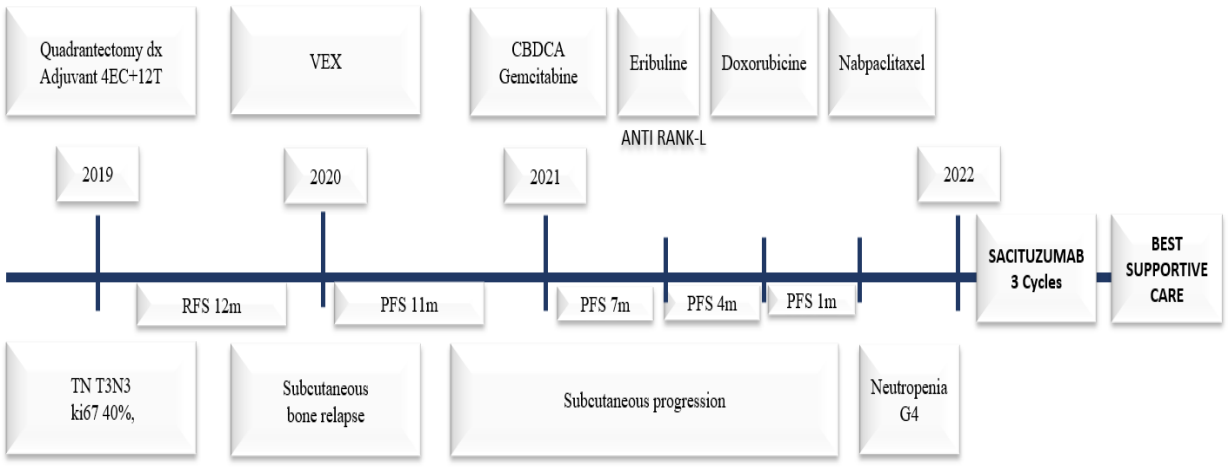

Figure 1: Breast cancer treatments timeline.

During the next two months for a further subcutaneous progression (the nodules at that time spread occupying all the breast area bilaterally, few nodules on the back and shoulders), the patients started liposomal pegylated doxorubicin (30 mg/m2 1 q21, 1cycles) [16], but after the first 2 cycles because of a slightly skin progression and G4 neutropenia we decided to switch to nab paclitaxel (100 mg/m2 1,8,15q28;) [17]. The PET-TC scan did not detect visceral progression. After one months from nab paclitaxel the clinical situation was still progressing and scattered on the breast subcutaneous area as shown in Figure 2.

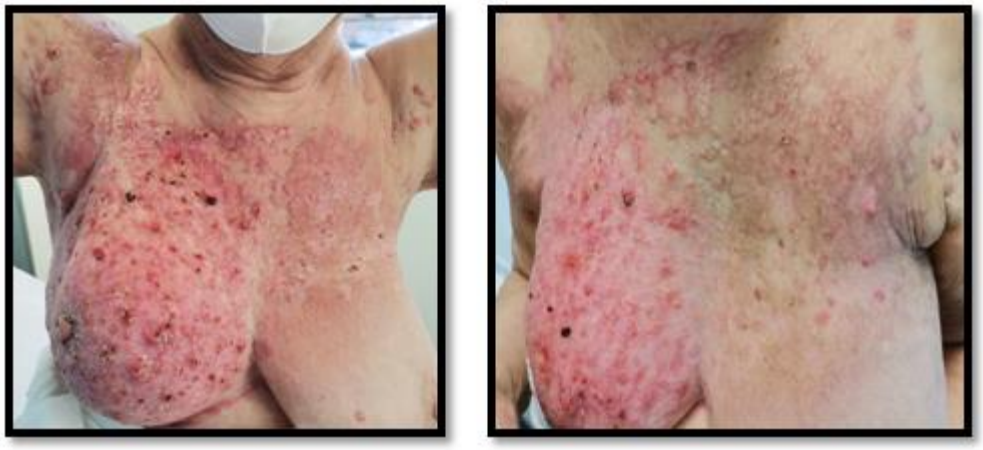

Figure 2: Picture of the cutaneous tumor breast spread before S.G. (left picture) and after first S.G. cycle (right picture).

Since the good clinical performance status and the skin-bony disease progressing, S.G was given such as part of the Expanded Access Program (EAP) as VI chemotherapy line, with the standard schedule (1,8q21). Considering the older age and the previous treatments the first cycle of S.G. was started with a lower dose (75%) and with support of granulocyte stimulating factor. The medications she was assuming were proton pomp inhibitor, enoxaparin (prophylactic dosage) and calcium 600 mg plus cholecalciferol 400 UI p.o. Before starting chemotherapy, the biochemical parameters were in normal range or presented at least a G1 alteration, such as creatinine clearance 52 mL/min and calcium that resulted 8.7 mg/dl (normal range 8.8-10.70). The first cycle seemed well tolerated in absence of clinical problems appearance and skin lesions resulted mildly responding (less hyperemic and flatter) but two days after C1d8, the patient was admitted to emergency department for persistent G3 diarrhea. Clinically she appeared asthenic, dehydrated and mildly suffering: hydration EV, and after excluding other cause of infections, loperamide 4 mg p.o, astringent diet, lactic ferments were given with a rapid resolution of the symptoms. Since the normalization of the laboratory parameters the second cycle was given, with further reduction of the dose (50%). At day 8 of the second cycle the laboratory assessment revealed a G4 hypocalcemia of 5.7 mg/dl (normal value range 8.6-10.2) and mild hypoalbuminemia 3310 mg/dl (normal value range 3400-4800), calcium correct for albumin of 6.26 mg/dl (normal value range 8.8-10.70), phosphorus resulted 2.26 mg/dl (normal value range 2.6-4.5), creatinine clearance 61 mL/min phosphates alkaline 224 U/l (normal value range 35-204), calcium assesses in the 24h urine sample 17.6 mg/24 h (normal value range 100-300), parathormone 756 pg/ml (normal value range 15-65), vitamin D 73.1 pg/mL (normal value range 19.9-79.3). Chemotherapy was discontinued and supplement of calcium and albumin was prescribed. Since the normalization of the parameters, after 15 days the third cycle was administered at 50% of the dose. Unfortunately, after seven days since the third cycle day 8, the patient was admitted to emergency department for G3 diarrhea concurrently with G3 asthenia and fever (38°C). The laboratory values revealed mild increasing of the creatinine (1.32 mg/dl NR 0.6-1), hyponatremia (133 mM/L, NR 136-145), and hypocalcemia G4 5.87 mg/dl (NR 8.6-10.2), the patient was admitted to the oncology in-patient department. Analyses of UGT1A1 resulted wild-type. The patient received a supportive treatment with fluid and electrolyte substitution, loperamide 4

mg, intravenously antibiotic in prophylaxis. She was discharged after 8 days, the patient referred an asthenia G1, the diarrhea was solved and calcium resulted 7.88 mg/dL (NR). After these events, accordingly with patient and her family, we decided to start best supportive care. The patient died 4 month after due to a respiratory insufficiency, likely due to pulmonary disease progression (Figure 3).

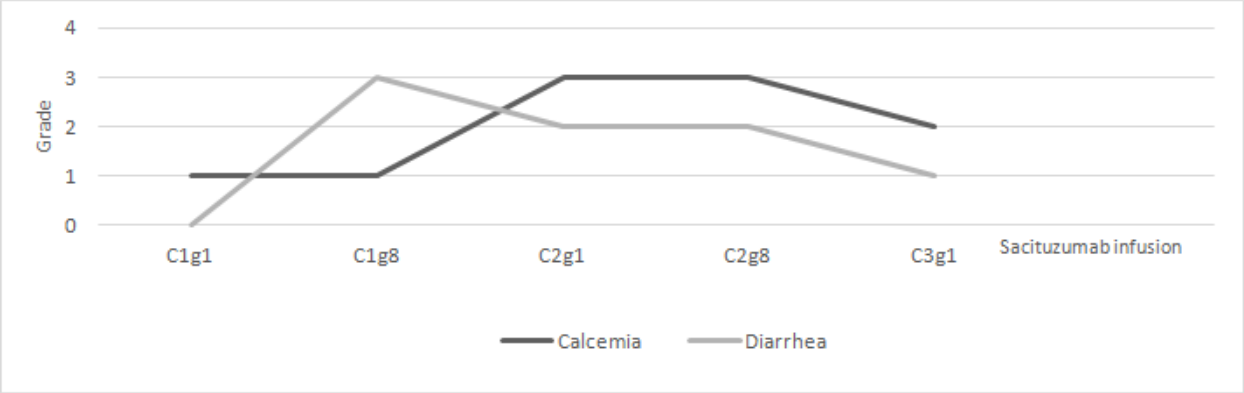

Figure 3: Time of hypocalcemia and diarrhea development according to S.G. cycles.

DISCUSSION

Sacituzumab govitecan is considered as an effective and generally well tolerated agent that represents a promising novel therapy for patients with mTNBC. This case report about highly pretreated elderly patient underlines how clinicians have to be aware about the symptom's management in particular to diarrhea and electrolyte alteration including calcium level, that should be monitored. Patients and caregivers should be advised of the risk of diarrhea, be instructed to immediately contact their healthcare provider if they experience diarrhea for the first-time during treatment or in the case of symptoms of dehydration such as lightheadedness, dizziness, or faintness; or inability to get diarrhea under control within 24 hours. In older patient these events can be more serious and faster developing, deeply impairing quality of life.

If patient develops signs of acute diarrhea or cholinergic syndrome (abdominal cramping, diarrhea, sweating, or excessive salivation) during or shortly after infusion, they should be treated with atropine 0.4 mg intravenous (IV) every 15 minutes for two doses, subsequent doses of atropine 0.2 mg IV may also be administered, for a total of 1 mg (FDA recommendation). Routine prophylaxis is not used if patient has not experienced diarrhea during the previous cycles. Infectious causes have to be considered and investigated at the onset of the symptoms before starting with loperamide. If ruled negative, promptly one dose of loperamide 4 mg p.o. and 2 mg p.o. after every additional episode of diarrhea for a maximum of 16 mg/day should be administered. An alternative approach, successfully used for irinotecan induced diarrhea, consists in 2 mg of loperamide every 2 hours or 4 mg every 4 hours at night [18]. Loperamide has minimal systemic absorption and is excreted in stool, so the risk of overdose is unlikely. In the drug data sheet of S-G, hypocalcemia of any grade (Grade 1 to 4 toxicity, G1-G4, Common Terminology Criteria for Adverse Events, CTCAE) is reported in 2 clinical studies [5,19] as a common adverse event occurring in 7.1% out of 366 patients treated with S.G while 0.8% reached a level lower than 7 mg/dL (G3-4).

A common cause of hypocalcemia is low level of albuminemia because calcium is linked by albumin and low level of albumin correlates with lower level of blood free calcium. The blood calcium level is maintained by hormones such as parathormone and calcitonin combined with active Vitamin D, in addition to dietary intake and renal-fecal excretion. A delicate balance between calcium, magnesium and phosphorus is also essential. The role of "Human trophoblast cell surface antigen 2" TROP-2, is deeply under investigation due to its role also as target therapy. This glycoprotein aberrant expression has been noted to serve an important role in the proliferation and migration of various types of human cancers. In preclinical model characterized by TROP-2 deficiency, its role to impair the differentiation of Mesenchymal stem cells (MSC) was described as correlated with significant reduction of adipogenesis and osteogenesis [20]. TROP-2 was also revealed as up-regulated in osteomalacia bone cells, introducing its potential role as a stimulator of MSC osteogenic differentiation. TROP-2 seemed to improve the bone structure by osteoblasts in a context of pathologic decrease of bone matrix mineralization which such as osteomalacia but also chronic kidney disease-mineral bone disorder or hypophosphatasia [21]. High expression of TROP2 was also observed in human osteosarcoma tissues and cell lines, promoting their spread and proliferation [22]. All these data according with the fact the TROP-2 is a calcium-transducing transmembrane glicoprotein also called "calcium-transducing transmembrane protein 2" could suggest a role in the bone-calcium homeostasis for TROP-2 regulation, which means S.G could influence this balance. Infact extracellular Ca2+-sensing receptor (CaSR) is most highly expressed in the parathyroid glands and kidneys to regulate circulating concentrations of Ca2+ (its calcitropic actions) but it is also expressed in other tissues where it is involved in noncalcitropic actions that include regulation of molecular and cellular processes such as gene expression, proliferation, differentiation and apoptosis. Abnormal expression or function of the CaSR in these noncalcitropic tissues has been reported to contribute to the pathogenesis of breast cancer. In breast cancer cells, the CaSR acts as an oncoprotein and increases proliferation and inhibits apoptosis, leading to an upregulation of PTHrP expression. Metastatic breast cancer cells in bone that express the CaSR might exacerbate PTHrP-mediated osteolysis by sensing high concentrations of Ca2+ released during bone remodelling and thereby promoting further PTHrP secretion. Thus, the CaSR has been hypothesized to drive a vicious cycle of skeletal metastasis [23,24].

Inhibiting TROP-2 and its CaSR function decrease proliferation of cancer cells but also production of PTHrP r and consequently reducing circulating concentrations of Ca2+, even this effect has not been previously described specifically for TROP-2. In general, the most frequent causes of hypocalcemia are linked to severe diarrhea or vomit, chronic renal insufficiency, hypo-parathyroidism and hypomagnesemia. In patient with cancer the main causes of hypocalcemia are: severe diarrhea and vomit due to chemotherapy, bone metastases, specific bone treatment such as anti-RANK ligand or bisphosphonates. Frequent electrolyte monitoring and possible Vitamin D and calcium replacement is mandatory in cancer patients. Symptoms of mild hypocalcemia can include muscle cramps, dry and scaly skin, brittle nails. Severe hypocalcemia can cause neurologic (affecting the nervous system) or psychologic (affecting the mind) symptoms, including confusion, memory problems, depression, hallucinations, irritability or restlessness till muscle spasms (including laryngospasm), tetany and arrhythmia. Treatment-related diarrhea of all grades was frequent with SG arm (any grade: 59%). Grade $\geq$ 3 diarrhea was reported in 10% of the

patients, median duration the episode of grade ≥ 3 diarrhea were 5 days and median times to onset were 19 days. No events of grade 4 or 5 diarrhea were described. In 55% of the patients concomitant treatment was used for diarrhea management; in most cases loperamide and in 10% of them atropine. Dose interruptions and dose reduction due to treatment-related diarrhea occurred in 5% of patients; no treatment discontinuations due to the treatment related diarrhea occurred.

Our case report describes a case of severe hypocalcemia consequent to Sacituzumab Govitecan, due to diarrhea toxicity but probably worsen for anti-TROP2 effect in calcium homoeostasis. In elderly patient the tenuous physiologic balance can be easier break when facing a chemotherapy and its toxicities. Patient and caregivers education, as well as correct medication and prompt supportive care are mandatory when starting Sacituzumab Govitecan.

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