



(CASE REPORT)



Stage IV Triple-negative breast cancer with brain and visceral metastasis has a complete response to sacituzumab govitecan: A Case Report

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Abstract

Background: Triple-negative breast cancer (TNBC) is a particularly aggressive subtype of cancer, characterized by its high propensity for metastasis. Patients who experience the development of brain metastases (BMs) and visceral metastasis face a challenging prognosis, as effective systemic treatment options for this specific condition are limited.

Case presentation: This case report describes the journey of a 42-year-old female patient diagnosed with left-sided triple-negative breast cancer with metastasis to the lymph nodes, bone, and brain. The patient underwent a combination of chemotherapy, immunotherapy, and targeted therapy, showing an initial response but subsequent disease progression. Multiple treatment modalities, including surgery, radiotherapy, including stereotactic radiotherapy, were employed to manage the metastases. The patient experienced complications such as anemia and hypocalcemia and received supportive care. Serial imaging, including positron emission tomography and MRI, were utilized for monitoring treatment response and disease progression documented.

Conclusion: The findings of this case report provide support for considering sacituzumab govitecan as a potential treatment option for recurrent and even BRCA-mutant triple-negative breast cancer (TNBC). Notably, sacituzumab govitecan demonstrated high activity in the presence of active bone and brain metastases.

Keywords: Brain metastasis; Triple-negative Breast cancer; Sacituzumab govitecan; Bone metastasis; Visceral metastasis

1. Introduction

Triple-negative breast cancer is characterized by the absence of three receptors: estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 (HER2)(1). This type of breast cancer constitutes around 15% of invasive breast cancers and is known for its aggressive tumor characteristics and unfavorable prognosis(2). It is more prevalent among younger women compared to older women and among black individuals compared to other racial and ethnic groups(3). Additionally, triple-negative breast cancer is frequently associated with metastases in visceral organs(4). Metastatic triple-negative breast cancer (mTNBC) has a median overall survival (OS) of only 12 to 18 months(3). For several years, chemotherapy has served as the primary systemic treatment choice for metastatic triple-negative breast cancer (mTNBC). Standard treatment regimens have traditionally involved the use of taxanes or anthracyclines as the initial approach in the first-line setting. (5).

Chemotherapy drugs have the ability to directly kill or impede the growth of tumor cells. However, these treatments can also impact normal cells within the body, resulting in significant systemic toxic side effects. (1, 6). This limitation

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poses a challenge to the broad utilization of chemotherapeutic drugs. Furthermore, genetic diversity, the development of chemoresistance, and the presence of tumor biological heterogeneity collectively contribute to the suboptimal response observed in many cases. Since TNBC lacks estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2), it is not sensitive to endocrine therapy or HER2-targeted therapy(7). Consequently, the treatment options for mTNBC are limited, particularly for patients who have not responded to both taxane and anthracycline therapies(8).

However, advancements in high-throughput sequencing technology have enhanced our understanding of the complexity and heterogeneity of TNBC(9). Several new targets have emerged, providing potential avenues for the treatment of mTNBC(10). These novel approaches involve disrupting the “three-dimensional structure” of “DNA double strands” using “trophoblast cell surface antigen 2 (Trop-2) antibodies”, inhibiting DNA damage repair, targeting the phosphoinositide-3 kinase (PI3K) pathway, preventing tumor cell binding to T cells, controlling the cell cycle, and more. These developments offer hope for improved therapies for mTNBC(11).

One such treatment option is Sacituzumab govitecan-hziy (IMMU-132; Immunomedics), it is an antibody-drug conjugate that combines SN-38, an active metabolite of irinotecan and topoisomerase I inhibitor, with the humanized monoclonal antibody hRS7 IgG1 κ , targeting the anti-trophoblast cell-surface antigen 2 (Trop-2)(12). This connection is facilitated by the cleavable CL2A linker(5). Trop-2, a transmembrane calcium signal transducer, is known for its overexpression in various epithelial cancers, stimulating cancer cell growth(13). It is found in breast cancer cells, including those in triple-negative breast cancer, with reports indicating its presence in more than 85% of tumors(14). When hRS7, either in its free form or conjugated to SN-38, binds to Trop-2, it is internalized by the tumor cell and delivers SN-38 to the site (15). Sacituzumab-bound tumor cells undergo intracellular uptake of SN-38, leading to their elimination. Moreover, the extracellular release of SN-38 contributes to the killing of adjacent tumor cells(16). This case report discusses a case of Triple-negative stage IV breast cancer with brain and visceral metastasis who showed a complete response to sacituzumab govitecan

2. Case Presentation

A 42-year-old female patient with no significant prior medical history presented with a diagnosis of left-sided triple-negative breast cancer. The initial assessment revealed a hypermetabolic breast mass, along with axillary, internal mammary, and supraclavicular lymph node metastasis, as well as right supraclavicular and mediastinal nodes without initial visceral metastasis. A positron emission tomography scan revealed limited metastasis. The patient's tumor marker levels were slightly elevated. The case was classified as stage IV limited disease and treatment was initiated. The case was discussed by a multidisciplinary team at Burjeel Hospital Previously, in May 2021, the patient began chemo-immunotherapy with Abraxane and atezolizumab. The treatment course lasted until November 2021, followed by maintenance atezolizumab. Histopathology conducted in May 2021 showed invasive breast carcinoma of no special type, high-grade intraductal areas, and a DCIS score of 3, grade 3. Lymphovascular invasion was not observed. The patient had estrogen receptor and progesterone receptor levels of less than 1%, HER2 score of 1% (low HER2), Ki-67 70-80%, and negative BRCA1 and BRCA2 gene mutations.

The patient received 8 cycles of atezolizumab, carboplatinum, and paclitaxel, starting in August 2022 and ending by the end of September 2022. The patient responded well to this treatment regimen. Later, a re-evaluation positron emission tomography scan was performed and it showed a new mediastinal lymph node that required mediastinoscopy. However, the histopathology of the lymph node revealed immune-related changes without signs of metastasis. The patient later experienced progression in the left breast, leading to a mastectomy and lymph node dissection in January 2022. Pathology results confirmed recurrent triple-negative breast cancer. Despite the recurrence, the patient continued on atezolizumab and received adjuvant radiotherapy to the left breast and axillary lymph node area.

Unfortunately, the patient developed aphasia, and an MRI of the brain revealed two small metastases. Stereotactic radiotherapy was administered to treat the brain lesions. The patient continued receiving atezolizumab but unfortunately showed progressive disease. However, the patient's positive HRR test indicated potential benefit from a PARP inhibitor. Therefore, the decision was made to continue treatment with carboplatinum and olaparib. Initially, this treatment was well tolerated, but the patient later developed symptomatic anemia, necessitating a blood transfusion.

An MRI of the brain conducted on August 8, 2022, revealed a previously noted left parietal cortex lesion measuring 4.5 x 3.2 mm, with peripheral enhancement and surrounding edema. No residual restricted diffusion was observed. Another previously noted small nodular lesion in the left parietal white matter showed significant septal enhancement, measuring 2 mm. Additionally, a new tiny nodular enhancing lesion was identified in the right cerebellum, measuring approximately 2.6 mm.

The positron emission tomography (PET) scan conducted on October 7, 2022, showed a regressive course of the previously identified left external iliac lymph node, indicating improvement. Additionally, there was complete metabolic resolution observed in the abdominal pelvic lymph node, indicating the disappearance of any metabolic abnormalities. The scan also revealed a mild metabolic progressive course in the mediastinal and hilar lymph nodes, suggesting some ongoing activity. However, there was a regressive course in the described FDG uptake in the T6-T7 and T8 vertebrae, with residual FDG present. Importantly, no other sites of metastasis were detected.

The patient was diagnosed with stage IV hormone-negative HER2 low +1 left breast cancer with metastasis to the lymph nodes, bone, and brain. To treat this, she underwent treatment with Abraxane, atezolizumab, carboplatinum, and paclitaxel, and was currently on olaparib. Additionally, she underwent left mastectomy, left axillary lymph node dissection, left breast and axillary lymph node radiotherapy, and stereotactic radiotherapy for a brain lesion. Secondary complications included anemia due to invasion of the bone marrow by malignant breast cells, as well as secondary malignant neoplasms in the bone. The patient also received blood transfusions and darbepoetin to address the microcytic hypochromic anemia.

On further examination, the tumor marker CA15-3 level was found to be elevated at 67. An MRI brain re-evaluation on December 23, 2022, revealed a suspicious area in the pre-center lesion at the S1 level. A computerized tomography (CT) scan conducted on December 13, 2022, reported an enlarging perihilar lymph node, which was identified as a bony metastatic lesion. At that time, the decision was made to continue Olaparib, and denosumab 120 mg was administered with a one-month follow-up appointment. Later, again patient presented with signs and symptoms of anemia, and her hemoglobin level was measured at 7.2. She received two units of blood transfusion to address the anemia.

The positron emission tomography (PET) scan conducted at Burjeel Hospital on January 27, 2023, revealed a metabolic progressive course in the previously identified FDG uptake in thoracic vertebrae 6-8, along with the presence of a newly developed multiple FDG avid intramedullary skeletal lesion, indicating bone metastasis. There was no evidence of visceral metastasis. Progressive disease was observed in multiple sites, including the left mediastinal external iliac node, and newly developed left cervical supraclavicular multiple mediastinal and abdominal lymph nodes. A focal increase was noted in the right cerebellum, suggesting the need for further investigation through an MRI brain. No FDG uptake was detected in the left mastectomy bed.

The MRI brain conducted at a private hospital on January 24, 2023, revealed that the right cerebellar lesion has increased in size and enhancement, showing septal restricted diffusion, indicative of a metastatic lesion. The absence of surrounding edema suggests dural metastasis. Additionally, there were two small suspicious foci of enhancement in the cerebellar vermis. There was evidence of treatment response with residual post-treatment changes in the left parietal lobe lesion. The patient reported undergoing focal radiotherapy, receiving 20 Gy in a single fraction to the right cerebellum on January 31, 2023.

The patient also experienced hypocalcemia, chemotherapy-induced neutropenia, anemia due to neoplastic disease and chemotherapy, functional dyspepsia, and herpes simplex on the upper lip. Denosumab was administered on February 8, 2023, and the tumor marker CA15-3 has increased to 118. Immune marker testing at a private hospital indicated a high percentage of Trop-2 and a low percentage of HER2. On the basis of these complications, the decision was made to discontinue Olaparib and sacituzumab govitecan was initiated.

The PET scan conducted at Burjeel Hospital on April 19, 2023, revealed a complete response to treatment. There was no evidence of newly developed FDG avid lesions. The previously observed hypermetabolic skeletal lesion showed complete metabolic resolution with sclerotic changes in the previously seen intramedullary lesions. Regression was noted in the multiple mediastinal and hilar lymph nodes. The FDG avid lymph nodes in the left cervical, left supraclavicular, and abdominopelvic regions also demonstrated complete metabolic resolution. The focal increased FDG uptake in the right cerebellum resolved as well. No new FDG avid lesions or distant metastases were observed. The diffuse activity in the bone marrow was attributed to chemotherapy or the growth factor filgrastim. The MRI brain performed at a private hospital on May 13, 2023, indicated post-radiotherapy changes with a small enhancing lesion in the left parietal region. The right cerebellar extra-axial focal enhancement had reduced in size compared to the previous image.

The current plan includes continuing sacituzumab govitecan. There has been a significant improvement in the hemoglobin level, leading to the discontinuation of darbepoetin and no more blood transfusion required. Additionally, there has been a significant improvement in liver function test results.

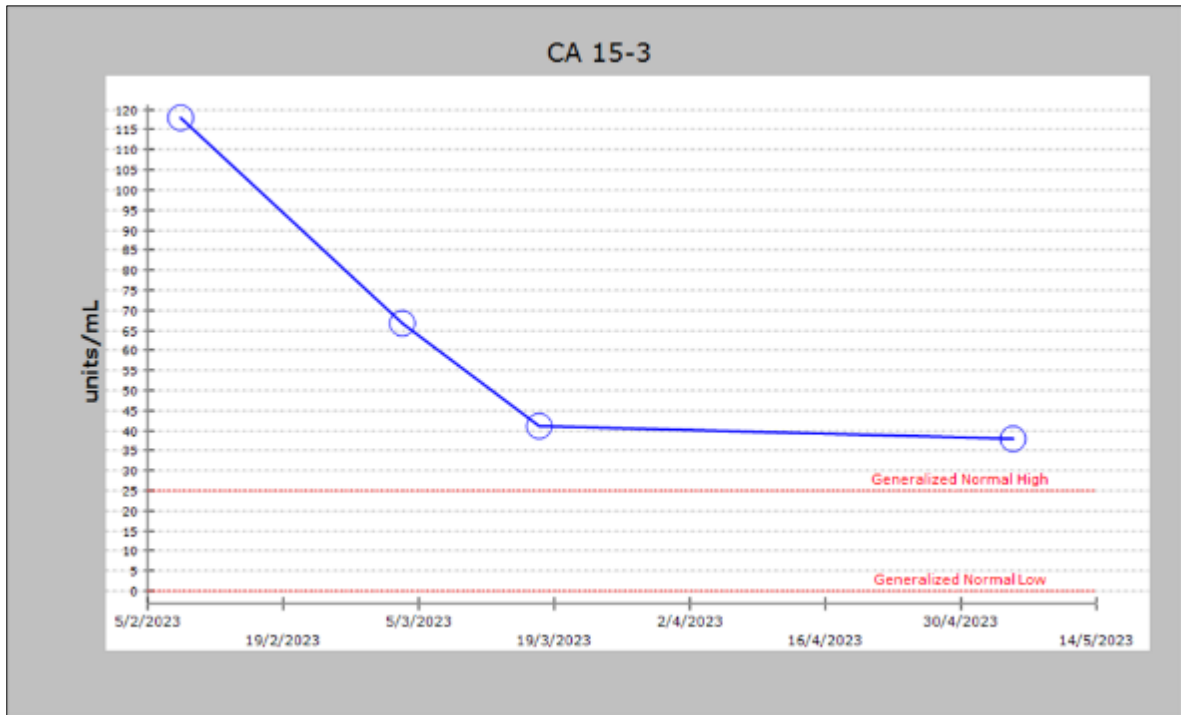


Figure 1a

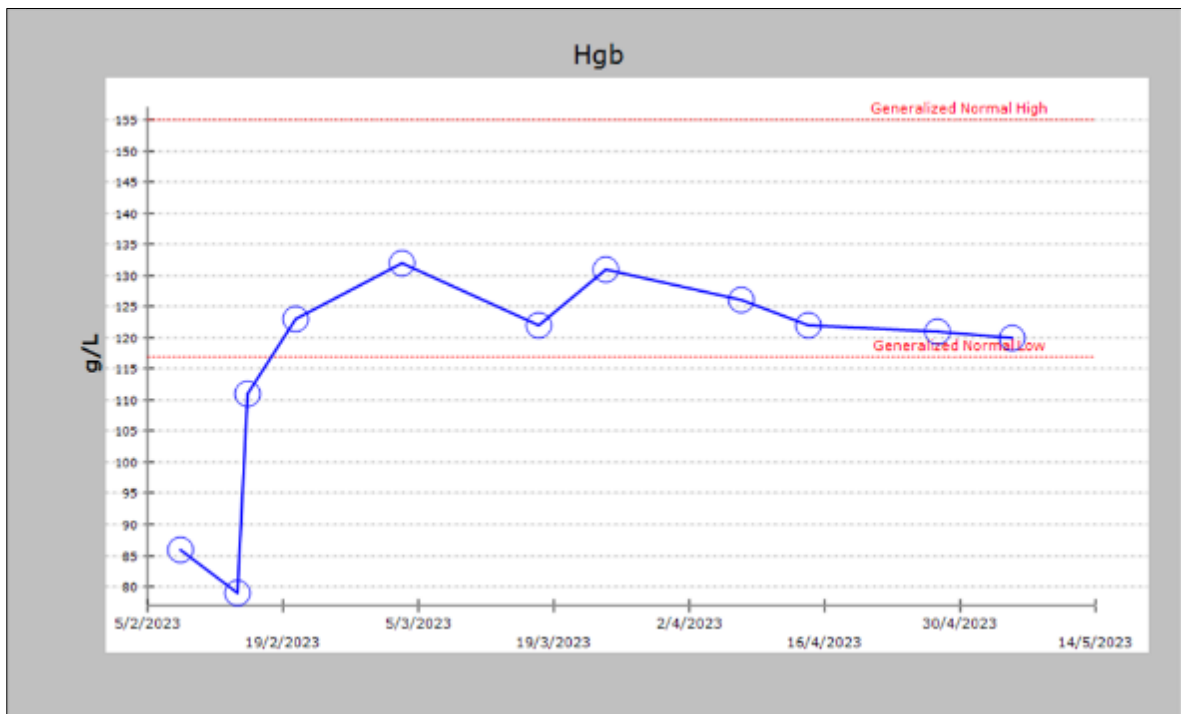


Figure 1b

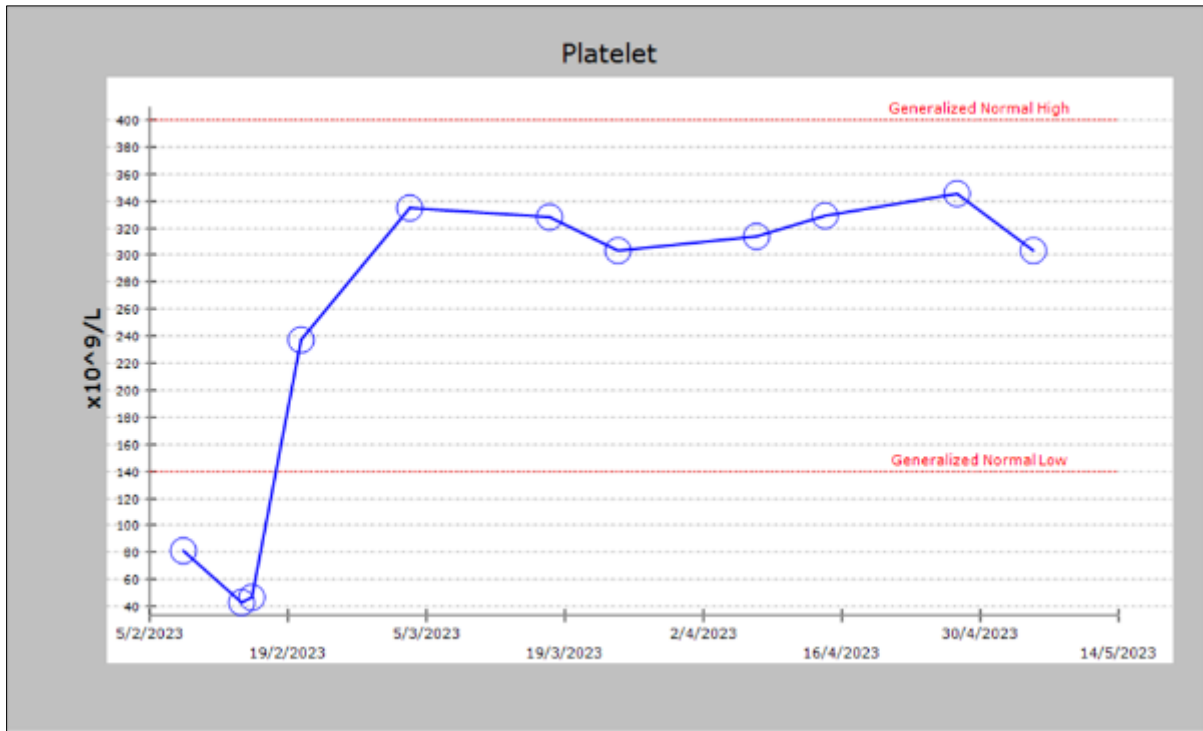


Figure 1c

Figure 1 a, b and c The above graphs showed improvement in tumor marker CA15-3 level and normalization of hemoglobin and platelet count after stopping olaparib and starting sacituzumab govitecan

3. Discussion

The case of the 42-year-old female patient with stage IV “triple-negative breast cancer” presents a complex and challenging scenario. Triple-negative breast cancer (TNBC) is an aggressive subtype characterized by the absence of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) expression (17, 18). This subtype tends to have a higher propensity for metastasis and poorer prognosis compared to other breast cancer subtypes. In our case, the patient's initial presentation revealed metastasis to various lymph nodes, including the axillary, internal mammary, supraclavicular, and mediastinal nodes. Further metastasis was observed in the bone and brain. This finding has been supported in research, in which bone, liver, and brain have been found to be the most common sites of metastasis in the clinical course of breast cancer, with frequencies of 70%, 30%, and 10-30%, respectively(19). The presence of bone metastasis (BM) in breast cancer patients often poses a significant limitation to their life expectancy and quality of life(20). Among hormone receptor-positive breast cancer cases, the incidence of BM is approximately 14% and the median survival time after BM diagnosis ranges from 9 to 10 months. Additionally, HER-2-positive breast cancer, which accounts for around 25% of cases, is linked with an increased risk of BM, ranging from 30% to 53%, and a median survival time of 11 to 18 months(21, 22).

According to Tham et al., aggressive pathological features pose a significant risk for the development of brain and bone metastasis (23). Notably, HER-2-overexpressing and triple-negative subtypes are particularly important risk factors for the occurrence of metastasis (24). In our case, the patient was triple negative breast cancer with negative HER2. Brain metastases in TNBC are linked with a poor prognosis, and their management requires a combination of local therapies, such as radiotherapy and surgery, along with systemic treatment options(25).

In our case, the patient's treatment course included the use of olaparib, a “poly (ADP-ribose) polymerase (PARP) inhibitor”, which was continued based on positive Homologous Recombination Repair (HRR) test results. PARP inhibitors have shown promise in patients with TNBC harboring BRCA1/2 mutations or deficiencies in the HRR pathway(26). However, the patient later developed symptomatic anemia, likely a result of myelosuppression from chemotherapy and bone marrow involvement by the breast cancer cells(27). Anemia is a common complication in advanced cancer and requires appropriate management, including blood transfusions. Our patient also received blood transfusions.

Due to different chemotherapy related complications doctors decided to discontinue olaparib and initiated sacituzumab govitecan therapy. Sacituzumab govitecan, an antibody-drug conjugate targeting Trop-2, has shown efficacy in heavily pretreated patients with metastatic TNBC who have developed side effects to PARP. In an exploratory sub-analysis of the ASCENT study, the efficacy of sacituzumab govitecan as a second-line treatment was evaluated specifically for patients who had received one line of therapy in the metastatic setting and experienced recurrence within 12 months after (neo)adjuvant chemotherapy prior to enrolling in the study(28). The findings regarding progression-free survival (PFS) and overall survival (OS) were consistent with the results of the ASCENT trial. Furthermore, a recent network meta-analysis demonstrated that sacituzumab govitecan outperforms other treatments in terms of all endpoints for patients with triple-negative breast cancer in the second or further lines of treatment(29). These findings, when considered collectively, provide strong support for considering “sacituzumab govitecan” as the preferred choice for “second-line treatment” in metastatic TNBC.

4. Conclusion

The findings of this case report provide support for considering sacituzumab govitecan as a potential treatment option for triple-negative breast cancer (TNBC). Notably, sacituzumab govitecan demonstrated high activity in the presence of active bone and brain metastases. It is worth noting that there is currently limited information available regarding the combination of radiotherapy and sacituzumab govitecan. Based on this evidence, it is suggested that sacituzumab govitecan may be considered in the systemic treatment sequence for metastatic TNBC. However, further real-world data and phase 3 studies are needed to confirm its efficacy and safety.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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