Clinical Oncology: Case Reports

Case Report

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Unusual Sanctuary Site (Central Nervous System) Metastases in Gastrointestinal Stromal Tumor Patients

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Abstract

Gastrointestinal Stromal Tumor (GIST) metastases occur in 18%-47% of patients and most commonly involve the liver and peritoneum. Central Nervous System (CNS) and other sanctuary site metastases are rare, with only limited single patient case reports available in the literature. Given the availability of multiple effective treatments and longer life expectancy in patients with metastatic GIST, there is an increased likelihood of metastases to sanctuary sites including the CNS. We sought to characterize three GIST patients who developed these rare sanctuary site metastases between 2017-2018 during their course of therapy and compare their clinical features and molecular profiles, to add to current knowledge and highlight the need for clinicians to consider sanctuary site metastases, particularly in patients presenting with new symptoms.

Keywords

Central Nervous System (CNS); Metastases; Gastrointestinal Stromal Tumor (GIST)

Introduction

Background

Gastrointestinal Stromal Tumor (GIST) is the most common mesenchymal neoplasm affecting the gastrointestinal tract. GIST metastases occur in 18%-47% of patients and most commonly involve the liver and peritoneum [1,2]. Less common sites of metastatic disease include the bone, lymph nodes, and lungs. Central Nervous System (CNS) and other sanctuary site metastases are rare, with only limited single patient case reports available in the literature.

There is a paucity of data regarding mutations seen in GIST patients with CNS metastases and most of these reports were in the era when treatment options were limited with few approved Tyrosine Kinase Inhibitors (TKIs). Of the published reports, the following mutations have been identified in GIST patients with CNS metastases: KIT exon 11 (2 patients), KIT exon 9 (1 patient), absence of mutation in either KIT or PDGFRα (1 patient). One of the aforementioned patients with an exon 11 KIT mutation in their primary tumor had an additional exon 17 mutations noted in their metastatic site [3-6].

Sanctuary site and CNS metastases in GIST patients have important treatment implications. Imatinib is a TKI specific for the tyrosine kinase domain in ABL, c-KIT, and PDGF-R. Following its approval for advanced GIST patients in 2002, it has transformed the management of GIST and altered the natural history of the disease. Imatinib is also used in chronic myelogenous leukemia and case reports in this disease have shown low penetration of imatinib into the cerebrospinal fluid in humans, suggesting that in patients with intact blood-brain barrier, poor responses of CNS tumors may occur with imatinib [7,8]. This concern for imatinib failure in GIST patients with CNS metastases is highlighted by a review of 7 patients with concurrent GIST and brain metastasis showing only 1 patient that responded to imatinib [3,9].

In this era with the availability of multiple TKIs and longer life expectancy in patients with metastatic GIST, there is an increased likelihood of metastases to sanctuary sites including the CNS. We sought to characterize three GIST patients who developed these rare sanctuary site metastases between 2017-2018 during their course of therapy and compare their clinical features and molecular profiles, to add to the current knowledge.

Methods

We identified patients treated at the University of Texas MD Anderson Cancer Center (MDACC) who developed sanctuary site metastases between 2017-2018 during their course of therapy. Retrospective evaluation of these patient's electronic medical record was performed by a clinician to identify: age at GIST diagnosis, primary tumor site, and size at time of initial GIST diagnosis, time to first metastasis, site of first metastasis, treatment before sanctuary site/CNS metastasis, time from metastatic GIST to sanctuary site/CNS metastasis, site of sanctuary site/CNS metastasis, presenting symptoms of sanctuary site/CNS metastasis, primary mutation, survival from time of initial GIST diagnosis, and survival from sanctuary site/CNS metastasis diagnosis.

Case Presentation

Three patients were identified that were treated at MDACC, who developed sanctuary site/ CNS metastasis between 2017-2018 during their course of therapy. Details of these individual patients are seen in Table 1 below. Demographically, all three patients were white females ranging from 49-55 years of age at the time of initial GIST diagnosis. Primary GIST was greater than 5 cm for all three patients (range: 9-26 cm) and the location was diverse (gastric, mesenteric, and rectal). The mitotic rate at the time of diagnosis ranged from 1/50 HPF (mesenteric primary) to 51/50 HPF (rectal primary) and was unknown at the time of diagnosis for the patient with gastric primary.

Synchronous metastases, defined as a metastatic disease within 3 months of initial GIST diagnosis, were seen in all three patients and two patients had metastases at diagnosis (liver in one patient and liver and lung in one patient). Subsequent metastases to sanctuary sites occurred 20-46 months following initial metastatic diagnosis (20, 39, and 46 months). Two of the three patients did not have symptoms at the time of sanctuary site metastasis diagnosis and these were instead

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Table 1: Clinical information for GIST patients with sanctuary site metastasis.

Age at Diagnosis (years)	Primary Tumor Site and Size	Time to First Metastasis and Site (s)	Treatment prior to CNS Metastasis (Best Response)	Time from Metastatic GIST to CNS Metastasis and Site	CNS Presenting Symptom	Treatment post CNS Metastasis (Best Response)	Primary Mutation	Status (Survival from initial diagnosis; from CNS metastasis diagnosis)
49	Mesenteric, 18.4 cm	77 days, lung	Imatinib (PD), Sunitinib (PD), Regorafenib (PD), Nilotinib (PD), Investi-gational TKI (PD), Dasatinib (SD)	39 months, epidural soft tissue mass at T7-T8	NA-noted on planned restaging	Radiation planned	PDGFRA exon 18, codon 842 (D842V)	Alive with disease (42 months; 11 days)
53	Gastric, 26 cm	0 days, liver	Imatinib (PR), Sunitinib (PR), Regorafenib (SD), Investi-gational TKI (PD)	46 months, left inferior rectus muscle	Vision changes	None (died 4 days after CNS metastasis diagnosis)	c-KIT mutation in exon 11	Deceased (46 months; 4 days)
55	Rectal, 9 cm	0 days, liver	Imatinib (SD), Investi-gational TKI (SD)	20 months, right skull base and epidural soft tissue disease spanning C3-C5	NA-noted on planned restaging	Radiation (PR), Sunitinib (PR)	c-KIT mutation in exon 11, TP53 mutation	Alive with disease (27 months since initial GIST diagnosis, 226 days since CNS metastasis diagnosis)

*SS: Sanctuary Site; PR: Partial Response; SD: Stable Disease; PD: Progressive Disease; NA: Not Applicable
Clinical features and molecular profiles of three GIST patients who developed sanctuary site/CNS metastases between 2017-2018 during their course of therapy, obtained from review of the electronic medical record

identified on planned restaging. One patient had vision changes preceding their diagnosis of sanctuary site metastasis. The exact site of sanctuary site metastasis varied and included epidural soft tissue metastasis at T7-T8, left inferior rectus muscle metastasis, right skull base metastasis, and epidural soft tissue disease spanning C3-C5. With regards to mutation status, two patients had a primary c-KIT mutation in exon 11, while the third patient had a PDGFRA mutation in exon 18 (D842V). One patient died 4 days after the diagnosis of metastasis to the left inferior rectus muscle, while two patients remained alive with disease at the time of last follow up.

With regards to treatment, all three patients had received TKIs, with a range of 2-6 regimens, before sanctuary site metastasis. No patients received definitive resection before their diagnosis with metastatic disease; however, two of the three patients did receive surgery following their diagnosis with metastatic disease. The patient with the rectal GIST primary underwent an abdominopelvic resection as well as a liver embolization following metastatic diagnosis. Meanwhile, the patient with the mesenteric GIST primary underwent partial gastrectomy and left lower lobe pulmonary resection. The patient with gastric GIST primary did not undergo surgery for her disease. As part of treatment for metastatic disease, all patients received imatinib with varied time on treatment from 1-10 months before progression. Treatment for sanctuary site metastasis included radiation to the right skull base and C3-C5 in one patient and switch to sunitinib with a partial response. Another patient was being planned for radiation treatment but had not undergone this treatment at the time of chart review.

Discussion

CNS and sanctuary site metastases have been rarely described in GIST patients, however increasing life expectancy with access to more TKIs to control the systemic disease may lead to increased frequency of metastases to sanctuary sites. This case report highlights three patients with GIST identified over 1 year that developed sanctuary site metastasis during their treatment at MDACC. While a small number, given the rarity of this development, this represents one of the largest reported single institution subsets of GIST patients with sanctuary site/CNS metastases currently published. Clinicians should be aware, so they can order appropriate staging in the setting of any suspicious symptoms.

All three patients described in this case report with sanctuary site metastases had high-risk disease features, including tumor size >5 cm. Of note, all three patients were Caucasian females aged 40-50 years with good performance status. One patient notably had a low mitotic rate of only 1/50 HPF, but with a large primary GIST (18.4 cm) in the mesentery. This suggests that pre-determined GIST risk features for metastatic spread, including anatomic site, size, mitotic rate, and tumor rupture may be useful when considering patients at risk of sanctuary site metastases. All three patients that were identified did have a substantial amount of time with the metastatic disease before their diagnosis with sanctuary site metastasis, ranging from 20-46 months. Additionally, while mutations are known to be of significant importance in resistance to TKI therapy, our data combined with available case reports in the literature suggests that the type of primary mutation does not seem to change the predilection for sanctuary site metastases.

With regards to the identification of patients with sanctuary site metastases, our patient's presentations were varied, with one patient with vision changes and the other two patients identified on planned restaging. Of note, CNS imaging or CT chest is not routine in GIST patients but was part of planned staging in these patients as part of their investigational therapy. As highlighted in these cases, CNS metastases can happen in GIST patients, particularly in patients with a significant length of time with metastatic disease, and unusual symptoms should prompt imaging of the area. Treatment usually includes switching to an alternate TKI, especially if there are other sites of progression and should include evaluation for local therapy at these sanctuary sites for symptom relief.

Conclusion

GIST sanctuary site metastases are rare. We present three GIST patients who developed sanctuary site metastasis between 2017-2018 during their course of therapy. Given effective treatment available, patients can have a prolonged course with metastatic GIST and clinicians must consider sanctuary site metastases, especially in patients presenting with new symptoms.

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