Hypoglycemia in a Patient With Metastatic Gastrointestinal Stromal Tumor: Is Chemotherapy a Reasonable Option for Symptom Control?

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ABSTRACT

Tumor induced hypoglycemia is a rare paraneoplastic phenomenon. However, hypoglycemia may also occur in solid tumors of epithelial or mesenchymal origin. Hypoglycemia caused by these types of tumours is referred to as non-islet cell tumour hypoglycemia (NICTH). Sunitinib is a drug that novel, oral, multitargeted tyrosine kinase. The biologic bases of the activity of sunitinib in patients with GISTs that are target multiple signaling pathways in tumor, stromal, and endothelial compartments.

In this report, we describe a case of metastatic gastrointestinal stromal tumor (GIST) presented with loss of consciousness due to hypoglycemia caused or worsened by sunitinib. In our opinion, who the patients with imatinib mesylate and sunitinib malate intolerant GIST, combination chemotherapy consisting of cisplatin and etoposid can be useful in the palliative setting, like our case.

Keywords: Hypoglycemia, Gastrointestinal Stromal Tumor, Chemotherapy

ÖZET

Hipoglisemi Gelişen Metastatik GIST Hastasında Semptom Kontrolü için Etkin Seçenek Kemoterapi Olabilir mi?


Anahtar Kelimeler: Hipoglisemi, Gastrointestinal Stromal Tumor, Kemoterapi
INTRODUCTION

Tumor induced hypoglycemia is a rare paraneoplastic phenomenon. However, hypoglycemia may also occur in solid tumors of epithelial or mesenchymal origin. Hypoglycemia caused by these types of tumors is referred to as non-islet cell tumor hypoglycemia (NICTH).1 Worsening of hypoglycemia in patients with NICTH might be caused by sunitinib treatment. In this report, we describe a case of metastatic gastrointestinal stromal tumor (GIST) presented with loss of consciousness due to hypoglycemia caused or worsened by sunitinib. In patients with imatinib mesylate (Gleevec®) and sunitinib malate (Sutent®) intolerant GIST, combination chemotherapy consisting of cisplatin and etoposide can be useful in the palliative setting.

CASE REPORT

A 51-year old woman who underwent resection of a large abdominal mass arising from the stomach was admitted in our hospital. At that time imaging showed multiple liver lesions and a mass arising from the stomach, histologically diagnosed as a high-grade metastatic leiomyosarcoma of liver biopsy. Ifosfamide 2 mg/m² day IV on days 1 through 3, Mesna 2 mg/m² day IV on days 1 through 3 and Doxorubicin 50 mg/m² day IV on day 1, six cycles were administered in 3-week intervals.

Three years later core biopsy demonstrated a CD 117-positive, (CD 117+ CD34+, keratin-hep-par-desmin-) spindle-cell tumor, consistent with a GIST. She was placed on Gleevec, as there was evidence of multifocal disease. Seven weeks after she gave up the drug because of intolerance. Dose modification and the dosing time of imatinib was changed from an evening dose to a morning was made, but she didn’t tolerate. The patient experienced recurrent episodes of nausea and vomiting. For that reason, gleevec was withdrawn and sunitinib mesilate was started. Two months later, her clinical status deteriorated, and she was hospitalized for dehydration, vomiting, and mental status changes, with blood glucose concentrations as low as 24 mg/dL (normal range 60 to 100) which could only be resolved with glucose 20% infusion. Further laboratory investigation showed normal kidney and liver function tests and low insulin (≤ 0.05 mU/l normal range 2-25 µIU/ml), low IGF1 (= 0.05 mU/l normal range 2-25 µIU/ml), low C-peptide (= 0.82 ng/ml normal range 1.77-4.68 ng/ml) levels. She recovered quickly after glucose infusion. A carbohydrate rich diet could hardly prevent more hypoglycemic events and prednisolone 30 mg per day was started. Liver metastasis progressed, than cisplatin (75 mg/m² on day 1 intravenously (IV)) and etoposid (100 mg/m² day IV on days 1 through 3) was started. Six cycles were administered in 3-week intervals. At that time she didn’t experienced any hypoglycemic events. Stable disease was established on third month HU reduction on CT scan (Figure 1 and 2). We know that change in the density of lesions on CT scan may be a good indicator in early, quantitative tumor response evaluation. Figure 1 CT imaging shows that the pretreatment contrast-enhanced CT scan shows a liver mass with relatively high attenuation (60 HU). The attenuation of the tumor after treatment has decreased (40 HU) (Figure 2).

Three months later local tumor progression was detected by CT scan and physical examination. At that time, debulking of the tumor was performed. Post operative 2 days after she died.

DISCUSSION

Our patient is a 51-year-old woman who underwent core biopsy of a large abdominal mass arising from the stomach, histologically diagnosed as a high-grade metastatic leiomyosarcoma of liver biopsy. The pathological examination showed that CD 117-positive, spindle-cell tumor, consistent with a GIST.

Until the development of imatinib, there has been no standard therapy for GIST. Doxorubicin and ifosfamide are the two most active agents in sarcoma. However, these two agents have limited activity in patients with GISTs. Based on the disappointing results with conventional agents, it has been difficult to recommend any particular agent or combination of drugs as standard care for metastatic GIST. The resistance of GIST to chemotherapy is currently unknown. It is interesting to speculate that oncogenic activation of KIT in GIST may contribute to chemoresistance through upregulation of antiapoptotic signaling or activation of other drug resistance mechanisms.
Sunitinib (SU011248) is an oral small molecular tyrosine kinase inhibitor that exhibits potent antiangiogenic and antitumor activity. Sunitinib demonstrated robust antitumor activity in preclinical studies resulting not only in tumor growth inhibition, but tumor regression in models of colon cancer, non-small-cell lung cancer, melanoma, renal carcinoma, and squamous cell carcinoma, which were associated with inhibition of VEGFR and PDGFR phosphorylation.\(^2\)

The introduction of targeted drugs in the clinic has resulted in unusual adverse effects such as hypothyroidism and hypoglycemia. Desai et al. reported that 62% of patients had an abnormal level of thyroid-stimulating hormone and 36% had hypothyroidism during treatment with sunitinib for gastrointestinal stromal tumors\(^3\) (GISTs). Regarding the pathogenesis of sunitinib induced hypothyroidism, several possible mechanisms have been suggested the role of VEGF in thyroid signaling is uncertain. Other factors, such as platelet derived growth factor and cKit, have roles in thyroid homeostasis, but so far no data have been published.\(^4,5\)

There are several mechanisms by which solid tumors can cause hypoglycemia\(^6\); insulin secreting insulinomas\(^7\), non-islet cell tumors secreting aberrant IGF-II and\(^8\) liver and adrenal failure due to tumor invasion. Hypoglycemia caused by solid tumors of epithelial or mesenchymal origin is referred to as non-islet cell tumor hypoglycemia (NICTH). NICTH is generally attributable to the secretion of large amounts of incompletely processed insulin-like growth factor II (IGF-II), also called ‘big’-IGF-II.\(^7\)

Soft tissue sarcomas have been associated with NICTH in several reports, including the first in 1930\(^8\) Most case reports and a systematic review on patients with mesenchymal tumors and NICTH date from the pre-GIST era and might therefore have missed this recently established diagnosis. Abdominal sarcomas (including spindle-cell sarcomas and leiomyosarcomas) of various histological subtypes which could well represent GIST’s.\(^9\) NICTH is an infrequent cause of hypoglycemia in patients with advanced cancer. Recently a few patients with advanced GIST and NICTH have been reported.\(^6,10-12\) NICTH is described in the secretion of large amounts of incompletely processed insulin-like growth factor II (IGF-II).\(^13\) Data on the exact incidence of NICTH are not available. It has been estimated that NICTH is four times less common than insulinoma, but the true incidence is probably higher. The most common histological types causing hypoglycemia are fibrosarcomas, mesotheliomas, leiomyosarcomas, and hemangiopericytomas. Laboratory inves-

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**Figure 1.** CT Imaging: The pretreatment contrast-enhanced CT scan shows a liver mass (arrow) with relatively high attenuation (60 HU)

**Figure 2.** CT Imaging: Response evaluation after treatment. The attenuation of the tumor has decreased (40 HU)
tigation can confirm the diagnosis NICTH. Low insulin and C-peptide levels are detected, related to a low glucose concentration. GH, IGF-I levels are typically decreased. An elevated level of IGFBP-2 is also a characteristic finding in patients with NICTH, although the mechanisms by which it is increased are unclear.

Measurements of insulin, proinsulin, c-peptide, were lower than normal levels. Suspicions arose for tumor-secreted insulin-like factor. Hypoglycemia is most often observed in presence of insulinoma and only isolated case reports in GIST patients exist.

Paraneoplastic syndromes occur in only 15 per cent of patients with known malignancies (e.g., lung cancer and metastatic carcinoid), and are rarely reported in the setting of GIST. Overexpression of insulin-like growth factor II is thought to be the mechanism of action. In order to treat the hypoglycemia, a short-term effect is best achieved with infusion of glucose and dietary guidelines. The best long-term treatment is to reduce the tumor by surgery, irradiation or chemotherapy. In our patient, frequent carbohydrate rich meals could not prevent the recurrence of new hypoglycemic events. Dietary measurements, glucocorticoids, GH and infusion of glucose could not sufficient.

NICTH should be considered in patients with GIST and hypoglycemia. Imatinib is likely to have contributed to the severity of the hypoglycemia given the inverse relation between glucose and imatinib concentrations. Worsening of hypoglycemia in patients with NICTH might be caused by sunitinib treatment, but additional investigations on the precise effects of sunitinib on glucose metabolism are warranted. In patients with imatinib mesylate (Gleevec) and sunitinib malate (Sutent) intolerant GIST, combination chemotherapy consisting of cisplatin and etoposid can be useful in the palliative setting.

REFERENCES


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