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Liver transplantation for metastatic wild-type gastrointestinal stromal tumor in the era of molecular targeted therapies: report of a first case

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Abbreviations

CT, computerized tomography; (WT-)GIST, (wild-type) gastrointestinal stromal tumor; LT, liver transplantation; MRI, magnetic resonance imaging; mTORi, mammalian target of rapamycin inhibitor; PDGFRA, platelet-derived growth factor receptor A; PET, positron emission tomography; SDH, succinate dehydrogenase; TKI, tyrosine kinase inhibitor.

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Abstract

The gastrointestinal stromal tumor (GIST) is a digestive neoplasm of mesenchymal lineage. The treatment strategy for receptor tyrosine kinase-mutated GISTs is well defined. Wild-type GISTs (WT-GISTs) respond unsatisfactorily to specific kinase inhibitors. Moreover, evidence shows that repeat surgery has limited benefit.

We report the case of a young female patient who was diagnosed with liver metastatic WT-GIST, after initial radical resection and adjuvant therapy with molecular targeted drugs. Due to the disease progression, a two-stage surgery was performed, with the removal of extrahepatic lesions followed by a total hepatectomy. The patient is disease-free after four years from liver transplantation (LT), performed under everolimus-based immunosuppression.

The treatment of WT-GISTs remains a significant challenge due to the frequent resistance to tyrosine kinase inhibitors (TKIs). Liver transplantation might represent an effective treatment option for such disease.

Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasm of the digestive system. These tumors normally result from a gain-of-function mutation in receptor tyrosine kinases, such as, most commonly, cKIT or the platelet-derived growth factor receptor A (PDGFRA). In the less frequent WT-GIST, the usual set of mutations is absent. Furthermore, a subset of WT-GISTs exhibits succinate dehydrogenase (SDH) deficiency and can occur either in syndromic or isolated presentation (1). WT-GIST is mostly indolent, is sited more commonly in the stomach, and it primarily affects young female patients, which explains why this tumor is sometimes referred to as “pediatric GIST” (2). To date, the ideal therapeutic management has not been pinpointed and the treatment of metastatic disease is still a matter of debate (2). The effectiveness of partial and complete liver resection (meaning LT) for GIST liver metastases is still under investigation, taking into account the protocols based on TKIs (2,3). Several decades ago, Pichlmayr advocated for the potential role of LT in the treatment of both advanced and rare oncologic conditions (4,5).

We present an unusual indication of LT for liver-only metastases from WT-GIST.

Case report

A 25-year-old female patient underwent LT on January 30, 2015, for metastatic cKIT/PDGFRA WT-GIST (Figure 1). The histology is detailed in Table 1 and the clinical

timeline is displayed in Figure 2. The patient authorized reporting of her medical history for scientific purposes.

In April 2006, when the patient was 16-years old, a symptomatic primary cardiac tumor was diagnosed. The patient underwent partial gastrectomy followed by imatinib (Gleevec®, Novartis Europharm Ltd., Horsham, UK) 400 mg/day as adjuvant treatment. In July 2007, she presented with liver metastases. The kinase suppression treatment was switched to sunitinib (Sutent®, Pfizer Ltd., Sandwich, UK) (6-8). Later on, due to progression while on sunitinib, the disease was managed with nilotinib (Tasigna®, Novartis Europharm Ltd., Horsham, UK) 800 mg/day, and remained stable from January 2008 to July 2013. At that time, the biggest hepatic lesion increased from 5.8 cm to 6.5 cm. After an unsuccessful attempt with sorafenib (Nexavar®, Bayer AG, Leverkusen, DE) 800 mg/day, from November 2013 to October 2014, the patient was treated again with imatinib. In November 2014, chest computerized tomography (CT) scan and magnetic resonance imaging (MRI) revealed that the largest hepatic lesion had reached 10 cm. Fluor-18 fluoro-2-deoxy-DGlucose positron emission tomography (PET) scan showed suspicious areas of increased uptake around the lesser and greater gastric curvature. We excluded the possibility of an oncologically radical partial hepatectomy, due to the presence of multiple small bilobar lesions. However, the patient exhibited severe nausea, vomiting, and chronic pain in the right upper quadrant, only partially responding to analgesics. We thus considered two indications for debulking surgery: the first one was pain control by removing the hepatic lesion that invaded the diaphragm; the second one was exploring the peritoneal cavity and sampling all nodes showing uptake on the PET scan, in order to remove extrahepatic locoregional disease and to exclude the presence of peritoneal deposits or distant abdominal metastases. Surgery showed diaphragmatic invasion by segment-VIII lesion but no further abdominal spread (Figure 3). This nodule and the adhering diaphragm were resected *en bloc* to relieve the chronic pain and the procedure was completed with an extensive lymphadenectomy. Pathology showed invasion of three of the lymph nodes that were sampled. Postoperative imaging proved negative for extra-hepatic tumor spread.

Taking into account her young age and the time lapse between the first diagnosis of gastric GIST and the findings of surgical exploration (lasting nearly nine years), we considered lymph-node spread and focal involvement of the diaphragm not to be a contraindication to further liver surgery, as the disease had remained confined to the area surrounding the liver with no peritoneal or distant deposits. Hence, we envisaged a total hepatectomy (actually requiring LT). The compelling necessity for surgery in order to relieve symptoms prevented

us from simultaneously scheduling LT with debulking surgery, since our center has no program for living-donor liver transplantation.

Two months later, in January 2015, a successful deceased-donor right-split LT was eventually performed. Immunosuppression consisted of prednisone and everolimus, aiming at a target trough level of 5 ng/ml. An early biopsy-proven acute cellular rejection was treated using mycophenolate sodium. To date, semi-annual imaging workup has not yet shown any recurrence. Pursuant to current international clinical practice guidelines for GIST (9), this imaging schedule includes thoraco-abdominal CT scan and liver MRI. Thirteen years after the initial diagnosis and four years after LT, the patient remains disease-free. Liver tests are normal under double immunosuppression including mycophenolate and everolimus.

Discussion

We report an exceptional case of non-syndromic WT-GIST liver metastases treated with LT. In 75% of cases of GIST, the main oncogenic event is a gain-of-function mutation in the KIT receptor and, for another 15%, in the PDGFRA. In contrast, WT-GISTs, which represent the remaining 10% of GISTs, lack mutation in receptor tyrosine kinase. Conversely, these neoplasms show a deficiency in succinate dehydrogenase (SDH) or a variety of mutations (BRAF, KRAS, PIK3CA), which constitute the non-SDH-deficient group (1).

Given its potential as a curative treatment, surgery is the therapeutic mainstay for KIT-/PDGFRA-mutated GIST. However, for less surgically fit patients or in case of widespread disease, TKIs are generally considered safer than extensive surgery, and they markedly changed the natural history of relapsing or metastatic cases (6-8).

Well-known risk factors for KIT-/PDGFRA-mutated GIST progression are tumor size, mitotic count, and location of the primary tumor (10). Conversely, WT-GIST is ostensibly a diverse disease, and its evolution is not significantly impacted by surgery. This subtype also exhibits some typical features such as sparse sensitivity to TKIs, low aggressiveness and indolent presentation (2). The progression of WT-GIST is poorly predicted by traditional risk stratification and may be influenced more by tumor biology than by treatment (1,2). Both surgery and medical treatments are uncertain, as outcomes have not been thoroughly studied. Lymphadenectomy in surgical treatment for GIST is controversial and usually not indicated, since the rate of lymph node involvement is reported at around 1%, and lymph node metastases do not result in a poorer prognosis (11,12). However, it is worth noticing that youth, being female, and the presence of Carney syndrome are factors associated with lymph node metastases, which is consistent with our case.

In 2005, before the availability of TKIs, Cameron et al. reported two cases of LT in KIT-mutated GIST (13). Given the success of current pharmacotherapy, this therapeutic option has almost been forgotten. Thus, the role of LT, following unsuccessful attempts with TKIs, has not been explored anymore, not even in TKI-resistant subtypes of GIST (2).

Our strategy was based on a two-step approach. First, an explorative laparotomy was performed, for complete abdominal assessment, removal of concomitant extrahepatic disease, and definitive pathologic examination. Second, total hepatectomy and LT were performed under a low mammalian target of rapamycin inhibitor (mTORi)-based immunosuppression. This therapeutic approach, which is at variance with available literature, has already resulted in a four-year disease-free survival. Indeed, a relatively recent report from the National Institutes of Health has suggested that resections for WT-GISTs should be restricted to the initial procedure and that subsequent resections should be performed only to tackle symptoms. These conclusions were supported by the absence of improvement in progression-free survival with more extensive or serial resections. The authors observed that WT-GIST has an indolent behavior, and most patients survive despite disease progression (2). In this sense, our total hepatectomy/liver transplant approach, following two previous resections, is totally divergent. Yet, given our anecdotic experience, we can offer an alternative perspective. Essentially, patients suffering from WT-GIST are in their childhood or young adulthood. Is it ethical to offer them only the perspective of a lifelong disease, which is rather poorly controlled with pharmacological receptor inhibition? With regard to evidence-based clinical decision making, median follow-ups of paper concerning WT-GIST hardly exceed five years (2). Thus, short follow-ups do not allow us to draw definitive conclusions on potentially curative surgery for WT-GIST, while repeated surgery could cut the risk of oncological progression and give patients a longer life expectancy.

The choice of an mTORi for therapeutic immunosuppression was based on the known mutual cross talk between the mitogen-activated protein kinase (MAPK) pathway and the phosphatidylinositol 3-kinase-mTOR-mediated signal. This cell-signaling pathway stimulates key components of carcinogenesis, such as cell growth, proliferation, and survival (5). The MAPK pathway is activated via several different routes, including upstream growth factor receptor tyrosine kinases and downstream mutations in gene components and is reportedly inhibited by mTORis (14). For advanced WT-GIST, the efficacy of a treatment addressing this biochemical relationship is purely speculative. Nonetheless, when no other treatments are available or successful, compassionate use of known potentially effective agents should apply. This report indicates that further research is necessary in order to further sequence and

characterize tumor epigenetics and molecular targets of WT-GIST. New and better drugs are needed in order to ameliorate the prognosis of these patients.

The place of LT in the treatment of this disease should be clarified, in comparison with - or, more likely, in addition to - hepatic resection and TKIs, with reference to long-term results. A hard but potentially curative treatment, such as LT, should be offered to (often young) patients, taking into consideration that, so far, the only alternative is the perspective of chronic cancer. Indeed, LT is becoming a game changer in the treatment of other secondary liver malignancies (15,16) and LT from living donation is a resourceful approach in transplant oncology. Living-donor LT often constitutes the treatment of last resort in case of not-yet-validated indications, which, in many allocation systems, prevent such patients from being registered on the waiting list. Moreover, in the interest of safety, left-hemiliver living-donor LT has been proved safe in both donor and recipient (17). Potential donors in a familiar environment typically step up and accept hepatectomy for donation, considering the cancer-driven deterioration of their beloved. However, they should be confronted with their own surgical risks and the possibility of a later disease recurrence, which could undergo further treatment in most cases. Finally, living-donor LT does not affect the scarce deceased-donor allograft pool. Therefore, this practice offsets ethical disputes about the use of a scarce resource for unverified indications for LT.

In conclusion, we first transplanted a young patient for a TKI-resistant WT-GIST and we obtained a long-lasting disease-free survival, under a soft mTORi-based immunosuppression. We argue that this approach is potentially of significant value for long-term results in this subset of patients and should therefore be subjected to further appraisal.

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Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation.*

Figure legends

Figure 1. Pathological specimen of the liver WT-GIST metastases. Haematoxylin and eosin (H&E) staining (background, 10x; top left, 20x) and immunohistochemistry for CD117 (positive, middle left, 20x), DOG1 (positive, bottom left, 20x), CD34 (negative, top right, 20x), S100 (negative, middle right, 20x), and desmin (negative, bottom right, 20x).

Figure 2. Clinical timeline.

Figure 3. Imaging of the segment-VIII hepatic lesion invading the diaphragm (white arrows), before (A) and after (B) last resection. In the second set of images, only a residual collection is apparent in its place (white diamonds).

Table 1. Therapeutic scheme and pathology of cKIT/PDGFRA wild-type GIST

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Table 1. Therapeutic scheme and pathology of cKIT/PDGFRA wild-type GIST

Date	Surgical procedure	Pathology
29/04/06	Partial Gastrectomy. Lymphadenectomy.	3.5-cm-large mixed spindle-cell/epithelioid neoplasm of the cardia. Immunohistochemistry: CD117-positive, actine-negative, desmine-negative, S100-negative, CD34-negative WT-GIST. Mitotic count: 17/50HPF. 1-cm-large paracardial invaded lymph node. R0 resection.
04/12/14	*En bloc* resection of diaphragm-invading segment-VIII liver tumour. Extensive lymphadenectomy.	8.5-cm-large hepatic lesion: epithelioid WT-GIST. Mitotic count: 4/50HPF. 1-cm-large diaphragmatic WT-GIST metastasis. 1-cm-large lateral caval invaded lymph node. 1.5-cm-large invaded lymph node of the greater curvature. 6-cm-large invaded lymph node of the hepatic artery. R2 partial liver resection.
30/01/15	Liver transplantation.	Multiple bilobar hepatic epithelioid WT-GIST metastases with a diameter ranging from 0.2 to 2.5 cm. 0.1-cm-large portal vein invaded lymph node. R0 resection.
Abbreviations: WT-GIST = wild-type gastrointestinal stromal tumour; HPF = high power field.