Target therapy in gastrointestinal tract sarcoma: What is new?

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INTRODUCTION

Soft tissue sarcoma are a heterogeneous group of uncommon tumors (about 1% of all cancer diagnosis) arising mostly from embryonic mesoderm. Most soft tissue sarcomas occur in the limb or in the limb girdle, but they can also localize in the abdomen (retroperitoneal or visceral and intraperitoneal)\(^1\). The gastrointestinal tract can be affected by several types of soft tissue sarcoma: gastrointestinal stromal tumors and leiomyosarcoma are the most represented, but also liposarcoma, synovial sarcoma and primary Kaposi sarcomas have been reported in literature.

For several years gastrointestinal soft tissue sarcomas have been managed with a multimodal approach based on surgery and chemotherapy. Despite this, the five year overall survival in patients with soft tissue sarcoma remains only 50% to 60% and most patients die of metastatic disease\(^2\), which usually become evident within two to three years from the initial diagnosis. Nowadays the introduction of target therapy in the treatment of soft tissue sarcoma seems to offer a concrete chance of changing the natural history of these aggressive tumors.

GASTROINTESTINAL STROMAL TUMORS

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumour of the gastrointestinal (GI) tract. GIST growth is often driven by an activating mutation of the proto-oncogene KIT\(^3\), encoding for a receptor tyrosine kinase (c-KIT): immunohistochemical detection of the resultant protein is positive in 85%-100% of GISTS\(^3\). In February 2002, the US FDA approved the tyrosine kinase inhibitor Imatinib for the treatment of GISTS and...
nowadays Imatinib represents the treatment of choice for advanced inoperable or metastatic disease\textsuperscript{[20]}. Response rate to Imatinib in GISTs is related to tumor molecular alteration: if the mutation occurs in the intracellular juxtaparanode domain of c-Kit (exon 11 is mutated in 67% of c-Kit positive GISTs) the rate of response will be about 85%; mutation in exon 9, 13 and 17 (coding for external and tyrosine kinase domains) accounts for lower response percentages. Imatinib can be used also in c-KIT negative GISTs thanks to the inhibition of mutated PDGFRA, a tyrosine kinase receptor activated by binding with PDGF. Unfortunately, most PDGFRA mutations occur in the tyrosine kinase site (exon 18) which makes the tumor poorly responsive to Imatinib action\textsuperscript{[20]}. In the metastatic setting the daily dose of Imatinib can be either 400 mg or 800 mg (400 mg bid): trials comparing the two doses have pointed out how a higher dose improves progression free survival\textsuperscript{[8]} and can result in responses in patients whose disease progressed with 400 mg/d\textsuperscript{[9]}. Molecular analysis as an initial assessment for GISTs is important not only to predict the Imatinib response rate, but also to define the exact Imatinib dose to start with: recent studies have shown there is evidence of improved response rates for patients with exon 9-mutant tumors treated with 800 mg vs 400 mg Imatinib\textsuperscript{[9]}. The role of Imatinib in the adjuvant setting is still under evaluation: randomized data show that one year treatment with Imatinib 400 mg in radically resected GISTs with high and intermediate risk of recurrence improves progression-free survival (PFS)\textsuperscript{[18]}. The risk of GIST recurrence is actually based on the size of the tumor, the mitotic count and the site\textsuperscript{[19]}. Further investigations are needed to determine the exact length of adjuvant therapy and to evaluate the possible impact on overall survival (OS). As for side effects, Imatinib therapy is reported to be well tolerated at the explored doses: the main toxicities are oedema (74%), nausea (52%), diarrhea (45%), myalgia/musculoskeletal pain (40%), fatigue (34.7%), dermatitis/rash (31%), headache (26%) and abdominal pain (26%), and their occurrence depends on dose, age, sex, previous chemotherapy and performance status\textsuperscript{[3,12]}. Primary Imatinib resistance has been reported frequently in Kit exon 9 mutated GIST, while secondary resistance to Imatinib occurs more commonly in Kit exon 11 mutated GIST and it is usually due to secondary mutations clustered in the KIT ATP binding pocket and kinase catalytic regions\textsuperscript{[13,14]}. Sunitinib has been approved in the treatment of Imatinib resistant GIST and as a first line therapy for patients intolerant to Imatinib. The safety and the efficacy of Sunitinib in Imatinib resistant GIST has been demonstrated in an open-label phase I / II study\textsuperscript{[15,18]} and in a placebo-controlled phase III trial\textsuperscript{[17]}. The dose of Sunitinib usually acted in GIST treatment is 50 mg/d using the 4/2 schedule\textsuperscript{[15,17]}, which seems to be well tolerated. The major side effects experimented by patients treated with a standard dose are abdominal pain, nausea, fatigue, diarrhea and anorexia.

**LEIOMYOSARCOMA**

Leiomyosarcoma is the second most common mesenchymal neoplasm in the gastrointestinal tract after GISTs and they may arise either from the muscularis mucosae or proper muscle layer.

**LIPOSARCOMA**

Liposarcoma is the most represented soft tissue sarcoma and accounts for 15%-20% of all mesenchymal malignancies but it is exceedingly rare in the gastrointestinal tract. To our knowledge only 18 cases occurring in the gastrointestinal tract have been reported in the world. Only a few synovial sarcomas arising in the gastrointestinal tract have been reported: most of them are from the esophagus and the stomach. Synovial sarcoma can be either a biphasic or monophasic neoplasm: biphasic synovial sarcomas contain both epithelial cells arranged in glandular structures and spindle cells, whereas monophasic types are composed of spindle cells. This type of sarcoma presents, in more than 90% of cases, a typical chromosomal translocation, t (X;18) (p11;q11)\textsuperscript{[18]}, that causes the fusion of two novel genes: SYT (at 18q11) and SSX (at Xp11). It has been clearly pointed out how the SYT-SSX fusion subtype correlates both with the histologic subtype and the clinical behavior of synovial sarcoma\textsuperscript{[19]}. Patients with advanced or metastatic leiomyosarcoma, liposarcoma or synovial sarcoma whose disease progresses during or after chemotherapy with doxorubicin or ifosfamide have few therapeutic options and very limited life expectancy. Trabectedin (Yondelis or ET-743) is an antineoplastic agent initially derived from the Caribbean marine tunicate Ecteinascidia turbinata and now produced synthetically. It acts by binding DNA minor groove, disrupting the cell cycle and inhibiting cell growth. Trabectedin given as monotherapy (1.5 mg/m2 as a 24-h continuous infusion every 3 wk) is approved in Europe for use in patients with advanced soft tissue sarcoma, after failure of standard therapy (doxorubicin or ifosfamide). It also has orphan drug status in soft tissue sarcoma in the US and in ovarian cancer in the US and Europe. Phase II studies suggest that around 40% of soft tissue sarcoma patients, failing conventional chemotherapy, experienced long lasting tumour control (either objective response or stabilization of disease) when treated with Trabectedin. The median duration of the time to progression was 105 d, and the 6-mo progression-free survival was 29%. The median duration of survival was 9.2 mo. Leiomyosarcomas and liposarcomas (most of all mixoid and round-cell subtypes) appear particularly sensitive to the drug, which seems to also be active against synovial sarcoma (progression arrest rate: 61%). Toxicity mainly involved reversible asymptomatic elevation of transaminases and neutropenia, both mild and manageable\textsuperscript{[20-22]}. Trabectedin is not associated with cardiotoxicity or neurotoxicity and alopecia is rare. Because of efficacy and tolerable toxicity profile, Trabectedin represents today an interesting new anticancer agent that offers much promise for the treatment of advanced soft-tissue sarcoma: ongoing studies are now evaluating the potential of Trabectedin as a neoadjuvant or a first line therapy, both alone or in combination with other cytotoxic agents and with modulators of intracellular signalling.
KAPOSI SARCOMA

Kaposi sarcoma (KS) is a multifocal, vascular lesion of low-grade malignant potential. Three clinical variants of Kaposi’s sarcoma have been identified: they all have identical histologic features but develop in specific populations and have different sites of involvement. The classic variant mainly affects elderly men of Mediterranean origin: it typically starts on the hands and feet and progresses up the arms and legs over a period of years, involving viscera in a small percentage of patients. The endemic variant affects African infants and young males and it is sometimes linked to human immunodeficiency virus (HIV) infection. The iatrogenic variant of Kaposi sarcoma is usually due to the treatment with immunosuppressive therapy for a variety of medical conditions, such as transplantation. Finally there is the epidemic, or acquired immune deficiency syndrome (AIDS)-associated, Kaposi’s Sarcoma, an aggressive variant involving lymph nodes, viscera, and mucosa as well as skin, that affect mainly young homosexual men [23]. Involvement of Kaposi’s sarcoma in the gastrointestinal tract is common in AIDS patients and can also occur in non-AIDS patients: while the gastrointestinal tract is a fairly common site of metastatic Kaposi’s sarcoma, primarily gastrointestinal Kaposi’s sarcoma is uncommon. Gastrointestinal Kaposi’s sarcoma can exclusively involve the upper (12%-24%) or the lower gastrointestinal tract (8%-12%) but it tends to be mostly multifocal [24]. The distinction between gastrointestinal Kaposi’s sarcoma and GIST can be difficult based only on microscopic aspects: young patient age, a history of immunosuppression, lamina propria infiltration, lymphoplasmacytic inflammation, extravasated red blood cells and haemosiderin deposition together with immunomarkers such as CD117, HHV8 and DOG1 may aid in the differential diagnosis [25]. Better understanding of the molecular events involved in Kaposi’s sarcoma has led to the identification of target structures for molecular tumor therapy. Kaposi’s sarcoma development usually requires infection with human herpesvirus (HHV)-8, known also as the Kaposi’s sarcoma-associated herpesvirus (KSHV) [26]. vGPCR is a G protein-coupled receptor encoded by KSHV whose dysregulation seems to play a fundamental role in KS development [27,28]. Several intracellular molecules have been shown to be activated in vGPCR-expressing cells: among these is the activation of the PI3K/Akt/mTOR pathway, identified as a critical signaling route in Kaposi’s sarcomagenesis. These data have been confirmed by the observation that Rapamycin (or Sirolimus), has emerged as an effective therapy for Kaposi’s sarcoma, at doses routinely used in immunosuppressive regimens. The immunosuppressive and antineoplastic effects of Sirolimus may be due to the inhibition of its molecular target (the mammalian target of Sirolimus, or mTOR), which causes a stimulation of protein synthesis and cell-cycle progression by activating a key enzyme in regulating gene translation: p70S6 kinase [29]. Indeed, Rapamycin has been shown to lower the secretion of vascular endothelial growth factor by preventing mTOR activation of the transcription factor HIF-1α [30]. Several recent studies have demonstrated that, in patients undergoing a kidney-transplant, the shift from cyclosporine and mycophenolate mofetil to the mTOR-inhibitor Sirolimus prevents the progression of Kaposi’s sarcoma, also providing an effective immunosuppression. Today we know that this drug is an efficient therapy not only for transplant recipients with (iatrogenic) Kaposi’s sarcoma [31,32] but also for patients with the classic form of the disease [33,34]. Unfortunately, the immunosuppressive action of Sirolimus makes its use in the treatment of AIDS associated kaposi’s sarcoma challenging: antiretroviral therapy in combination with chemotherapy (liposomal doxorubicin 6 cycles 20 mg/m² iv every 2 wk) is the first choice treatment in these patients. Among new target therapy for the treatment of Kaposi’s sarcoma we can include Bortezomib, which targets nuclear factor κB, Raf or MEK kinase inhibitors, functioning via MAPK and inhibitors of the Jak/STAT pathway. The tyrosine kinase inhibitor Imatinib has been also tested successfully in a 10 patient pilot study [35]. Another approach could consist of the inhibition of growth factors occupied by HHV8, such as VEGF throughout Soroafenib [36]. The matrix metalloproteinase inhibitor COL-3, an inhibitor of angiogenesis, was administered to 75 pre-treated patients and achieved dose dependent response rates of 29%-41% [37]. Further investigations are needed to assess the real potential of all these new biological therapies.

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