Imatinib

It is used in chronic myeloid leukemia (CML) treatment. Imatinib has contributed to complete and prolong cytogenetic responses so it is now the standard treatment of CML.

Recently, Imatinib mesylate has shown a significantly prolonged progression-free survival and overall survival in metastatic and locally advanced c-Kit positive gastrointestinal stromal tumors (GISTs) and more recently a prolonged disease-free survival in operated high-risk GIST.

In the case of locally advanced or metastatic chordomas, medical treatment is frequently discussed. While chemotherapy is ineffective, it would appear that some molecular targeted therapies, in particular imatinib, could slow down the tumor growth in case reports, retrospective series, and phase I or II trials. Nineteen publications, between January 1990 and September 2014, have been found describing the activity of these targeted therapies. A systematic analysis of these publications shows that the best objective response with targeted therapies was stabilization in 52 to 69% of chordomas. Given the indolent course of advanced chordoma and because of the absence of randomized trials, the level of evidence to treat chordomas with molecular therapy is low (level III), whatever the drug. Furthermore, we could not draw a firm conclusion on the activity of imatinib. Other putative targets have also been described. Therefore, further clinical trials are expected, especially with these targets. Nevertheless, it seems essential, in those future studies, to consider the naturally slow course of the disease [1)].

Neurodegeneration can be prevented by imatinib mesylate (Gleevec or STI571) which regulates c-Abl tyrosine kinases, which elicit protective effects in neurodegenerative disease models. However, the protective effect of STI571 against prion disease remains unknown. In the present study, the effect of STI571 on prion peptide-induced neuronal death was investigated. Results showed that STI571 rescued neurons from PrP106-126-induced neurotoxicity by preventing mitochondrial dysfunction. STI571-inhibited c-Abl tyrosine kinases prevented PrP106-126-induced reduction in mitochondrial potential, Bax translocation to the mitochondria and cytochrome c release. The protective effect of STI571 against mitochondrial dysfunction was related to the activation of BIM expression. This study is the first to demonstrate the protective effect of STI571 against prion-mediated neurotoxicity. Our results suggested that imatinib mesylate treatment may be a novel therapeutic strategy to treat prion-mediated neurotoxicity [2)].

Complications

Imatinib is a well-tolerated treatment with few side effects mainly gastrointestinal symptoms (nausea, vomiting, and diarrhea), headaches, rash and periorbital edema. Hemorrhage incidents are rare in patients treated with Imatinib. They are more frequently seen in CML patients. Hemorrhage incidents in CML include in many cases upper gastrointestinal (GI) tract bleeding and central nervous system bleeding in rare ones. In GIST patients treated with Imatinib, hemorrhage incidents are exclusively made of upper GI tract bleeding consecutive to tumor perforation or necrosis. In our observation, we present the case of a subdural hematoma occurring in a patient treated with adjuvant Imatinib for a high-risk localized gastric GIST. No other case of subdural hematoma in GIST treated with Imatinib has been reported in the literature [3)].

Imatinib (Gleevec®) (a tyrosine kinase inhibitor) has some antitumor effect in chordoma [4)].

The failure of hormonal and cytotoxic chemotherapy in the treatment of recurrent meningioma and increasing understanding of potential molecular targets in meningioma has resulted in multiple studies utilizing single-agent targeted therapy directed at biologically relevant signaling pathways, such as somatostatin (Sandostatin(®) LAR, SOM230c), PDGF (imatinib), EGF (erlotinib) and VEGF (sunitinib and vatalanib) [5].

Imatinib for glioblastoma

Imatinib for glioblastoma.

Secondary resistance

Secondary resistance to imatinib (IM) represents a major challenge for the therapy of gastrointestinal stromal tumors (GISTs). Aberrations in oncogenic pathways, including autophagy, correlate with IM resistance. Regulation of autophagy-related protein 5 (ATG5) by the ubiquitin-proteasome system is critical for autophagic activity, although the molecular mechanisms that underpin reversible deubiquitination of ATG5 have not been deciphered fully. Gao et al. identified USP13 as an essential deubiquitinase that stabilizes ATG5 in a process that depends on the PAK1 serine/threonine-protein kinase and which enhances autophagy and promotes IM resistance in GIST cells. USP13 preferentially is induced in GIST cells by IM and interacts with ATG5, which leads to the stabilization of ATG5 through deubiquitination. Activation of PAK1 promoted phosphorylation of ATG5 thereby enhancing the interaction of ATG5 with USP13. Furthermore, N6-methyladenosine methyltransferase-like 3 (METTL3) mediated stabilization of USP13 mRNA that required the m6A reader IGF2BP2. Moreover, an inhibitor of USP13 caused ATG5 decay and co-administration of this inhibitor with 3-methyladenine boosted the treatment efficacy of IM in murine xenograft models derived from GIST cells. These findings highlight USP13 as an essential regulator of autophagy and IM resistance in GIST cells and reveal USP13 as a novel potential therapeutic target for GIST treatment [6]

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