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Letter

Imatinib mesylate in patients with metastatic gastrointestinal stromal tumour relapsing after hepatic transplantation

Gastrointestinal stromal tumours (GIST) represent a morphological and immunohistochemical entity [1] that have a constitutionally active c-kit protein. In non-operable patients, before the drug imatinib mesylate was available, patients treated with chemotherapy had response rates under 10% and a median survival under one year. Liver transplantations have been anecdotally reported as a treatment option for patients with metastatic liver disease, but its impact has not been investigated in large patient cohorts. However, the development of the targeted agent imatinib mesylate has dramatically improved the outcome of metastatic GIST patients with long-term control rates of close to 50–70% being reported [2,3]. Whether imatinib can be used after liver transplantation when GIST patients have relapsed has not been reported. We report two clinical cases in which this treatment was found effective and feasible in this situation, albeit with an adaptation of the immunosuppressive treatment.

The first patient was diagnosed with a "primitive liver epithelioid leiomyosarcoma" in 1986 and received first-line chemotherapy, with no response, then a liver transplantation with cyclosporin as immunosuppressive treatment. Thirteen years later, this patient had a relapse in the form of a GIST that was unresectable. Their GIST showed CD117 expression and an exon 11 activating mutation within the transplanted liver was diagnosed. Imatinib treatment was started and cyclosporin concentrations were monitored concomitantly. Cyclosporin given orally at a dose of 250 mg daily prior to imatinib had to be decreased to 100 mg/day four months after the initiation of imatinib treatment. The patients is alive 24 months after the initiation of imatinib.

The second patient was diagnosed in 1995 with a primary mesenteric tumour with liver metastasis. Their disease was characterised as a CD117+ GIST with a deletion of nine base pairs in exon 11 of the KIT gene. Despite chemotherapy, the tumour progressed and a cadaveric liver transplantation was performed and tacrolimus was given as the immunosuppressive treatment. Two years later, a second unresectable relapse with multiple intrahepatic and adrenal metastases was diagnosed. Imatinib was started at a dose of 400 mg/day. Before the introduction of imatinib, the daily oral dose of tacrolimus was 2 mg, yielding plasma concentrations of 4.8 μg/l. After the initiation of imatinib treatment, the plasma concentration of tacrolimus increased to 14.2 μg/l. The dose of tacrolimus was decreased to 1 mg/day 2 months after the initiation of imatinib.

The aforementioned patients were selected to undergo liver transplantations because they had unresectable metastatic hepatic tumours. Following imatinib mesylate treatment, a reduction in the metastatic lesions and an improvement in the general status of the patient occurs as is typically observed with this agent. However, special attention must be paid to the concomitant administration of immunosuppressive treatment and imatinib mesylate. Cyclosporin and tacrolimus concentrations must be monitored closely in the first few weeks of imatinib treatment. This is because imatinib mesylate is mainly a substrate of the isoenzyme CYP3A4/5 cytochrome P450. Its metabolism may therefore be increased when drugs modulating CYP3A4 activity are co-administered [4]. Conversely, plasma concentrations of drugs may be increased by imatinib mesylate, since imatinib is a competitive inhibitor of this isoenzyme. So imatinib mesylate can be active in patients with relapsing GIST after liver transplantation, despite long-term immunosuppressive treatment, but increased plasma concentrations of immunosuppressive agents may lead to a reduction of 50–80% in the daily dose. Most likely, the plasma concentration of cyclosporin increases as a result of competition for the cytochrome P450 3A3/4 isoenzymes, while the plasma concentration of tacrolimus, which is mainly metabolised by CYP3A 4/5 [5], is increased by imatinib mesylate through the competitive inhibition of CYP3A.

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