Effective salvage therapy of imatinib-resistant gastrointestinal stromal tumor with combination of imatinib and pegylated liposomal doxorubicin


1. Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms of the gastrointestinal tract, resulting from mutations in c-kit and platelet derived growth factor receptor. GISTs can arise anywhere along the gastrointestinal tract but are most common in the stomach (50%) and small bowel (25%). The primary treatment is curative surgery. When GIST became metastatic, it is generally considered chemo-resistant. The most common metastatic site are liver and peritoneum. Imatinib, which inhibits the activated mutant c-kit and platelet derived growth factor receptor, has become the first line treatment of advanced GISTs. The initial standard dose 400 mg/day was considered to be safe and to achieve response induction. Dose escalation to 80 mg/day is a reasonable option for patients progressing on 400 mg/day. However, some patients possess primary resistance and others may develop secondary resistance after several months of imatinib treatment. We here report a case with metastatic GIST developed secondary resistance after imatinib treatment successfully treated with combination of imatinib and pegylated liposomal doxorubicin (PLD).

2. Case report

A 60-year-old Taiwanese man was diagnosed with an advanced GIST in March of 2008 after several months of abdominal fullness and poor appetite. A computed tomography (CT) guided biopsy of the abdominal mass was performed, and histopathological examination showed typical
features of GIST with positive CD117 immuno-staining. Imatinib 400 mg per day was prescribed with good response. However, a follow-up abdominal CT scan 7 months after imatinib treatment showed progressive change and new liver metastases. All recurrent tumors were resected in the December of 2008. Mutation analysis of KIT gene in all the resected tumors revealed deletion mutations of codons 558–565 in exon 11 (Fig. 1A), whereas a missense mutation was also identified at codon 822 in exon 17 in one resected tumor (Fig. 1B). The daily imatinib dose was then increased to 800 mg. Unfortunately, abdominal CT scan, one month later, showed tumor progression in the liver and peritoneal seeding. Palliative surgery was performed, and imatinib was continued at the same dose. However, generalized disease progression over liver and peritoneum was found three months later (Fig. 2A and B). Therapy was then changed to 400 mg

Fig. 1. Mutation analysis of all resected tumor showing codon 558–565 deletion in exon 11 in all resected tumor (A, arrow) and N mutation in exon 17 in one resected tumor (B, arrow).

Fig. 2. Computed tomography scan showed the treatment response of the tumor burden before (A and B, arrow, April 2009) and after (C and D, arrow, Jun 2009) administration of Liposomal doxorubicin.
imatinib per day plus dasatinib 70 mg twice a day, but the patient experienced increased ascites. Positron emission tomography scan showed high uptake of fluorodeoxyglucose 18 in the tumors. Dasatinib was discontinued, whereas imatinib was maintained at 400 mg per day. Furthermore, PLD50 mg/m² every three weeks was administered as salvage chemotherapy. The ascites remarkably improved after one dose of PLD administration. The follow-up abdominal CT scan 2 months later revealed a marked decrease of ascites and shrinkage of the liver and peritoneal metastases (Fig. 2C and D, indicated by the arrows). Unfortunately, a CT scan of the abdomen five months later (after 7 doses of PLD) revealed disease progression. Combination of imatinib and PLD resulted in a 5-month progression free period for this patient with imatinib-resistant GIST.

3. Discussion

Secondary resistance, which most often results from secondary mutations of KIT exon 13 or 17, is almost inevitable after imatinib treatment. For this case with exon 17 mutations, there are few treatment options available.9 Surgical intervention was performed for the first local recurrence, as recommended by previous publications.10,11 Unfortunately, as disease progressed, dasatinib was chosen based on its in vitro efficacy only.12—14 However, it did not produce any response and instead worsened patient’s condition. Previous studies failed to show efficacy of PLD alone in treating advanced GIST.15,16 However, in this particular case, combination of PLD with imatinib produced a dramatic response by halting the rapidly deteriorating disease course and inducing a sustained tumor-control period. PLD may indeed show efficacy in GIST when used in combination with imatinib. Furthermore, the use of PLD may result in a higher intra-tumor concentration of doxorubicin, which can overcome the chemotherapy resistance. The response seen in this patient is significant and provides evidence of clinical benefit of combining imatinib and PLD in treating imatinib-resistant GIST. This combination treatment warrants further study.

References


