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SHORT COMMENTARY

The Role of Adjuvant Therapy in Gastrointestinal Stromal Tumor after Operative Treatment

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Abstract: The treatment for localized advance gastrointestinal stromal tumor (GIST) is far from ideal. Up to 50% of patient developed post-operative recurrence and died within 5 years. Recently, imatinib was found to significantly improve recurrence-free survival in post-operative patients. The role of adjuvant therapy in high risk GIST patients is discussed.

Keywords: GIST, adjuvant, imatinib, operative

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The Role of Adjuvant Therapy in Gastrointestinal Stromal Tumor after Operative Treatment

Although gastrointestinal stromal tumor (GIST) is generally regarded as a rare tumor, it is the most common sarcoma in the gastrointestinal tract (GIT). The estimated annual incidence is about 1.5 per 100,000.[1] The tumor occurs typically in the stomach or small intestine, infrequently in the colon, rectum or esophagus, and rarely outside of GIT. It is unique in comparison with other solid malignancies in the way that its mechanism of development and molecular characterization is better understood. About 85% of such tumor had an activating mutation in the KIT proto-oncogene, whereas 3%–5% contains a mutation in platelet-derived growth factor receptor-alpha (PDGFRA).[2–4] This knowledge is essential for development of effective target therapy. Imatinib mesylate (Gleevec) is a selective molecular inhibitor of KIT, PDGFRA, ABL and BCR-ABL tyrosine kinases. It stops auto-phosphorylation of the receptor and thus halts tumor proliferation. The development of imatinib revolutionized the treatment for GIST as well as chronic myelogenous leukemia. In a phase III study, over 80% patients with metastatic GISTs responded to the treatment with Imatinib.[5] It becomes the standard therapy for patient with recurrent GIST after surgery or metastasis in various guidelines.[1,6]

A few controversial issues exist in the management of GIST. For patient with small upper gastrointestinal GIST (e.g. <2 cm in size), the best course of therapy is uncertain. Some experts recommend surgery for all because even small GISTs can occasionally metastasize, sometimes with a delay of many years.[7–8] However, it appeared to be an over-aggressive therapy for most patients with small indolent GISTs found incidentally during upper endoscopic examinations. Alternatively, regular endosonographic surveillance is recommended to detect any interval progression.[1] This strategy is found to be useful by some[9] but not the others.[10] Furthermore, the frequency of surveillance and threshold for intervention is not defined.

On the other hand, treatment for localized advance disease is far from ideal. Complete R0 surgical excision, without dissection of clinically negative lymph nodes, is the current gold-standard therapy for localized GIST.[1] However, up to 50% patients developed tumor recurrence and died within 5 years in a large series.[11] The most frequent locations for tumor recurrence are the liver and peritoneum. Mitotic figure >5/50 high power field, primary tumor size ≥10 cm and small bowel location were independent predictive factors for tumor recurrence after surgical resection.[12] Neoadjuvant treatment with imatinib for cytoreduction and allowing less mutilating surgery is recommended for advance invasive tumor.[1] Nevertheless, post-operative adjuvant treatment after complete tumor resection has not generally been recommended[13] or been considered investigational only[1] in view of absence of clinical data. Nisson B, et al performed a pilot study on adjuvant imatinib treatment.[14] In this study, 23 patients with malignant GIST received imatinib for one year after radical surgery. Only 1 patient developed recurrent disease during a mean follow-up over 3 years, in contrast to 32 out of 48 patients (67%) in the historical control group. Most recently, DeMatteo RP, et al performed a large scale randomized control trial on adjuvant imatinib treatment in over 700 patients with primary GIST.[15] The tumors were at least 3 cm in size and positive for KIT protein by immunohistochemistry. Adjuvant imatinib therapy was found to significantly improve recurrence free survival from 83% to 98% at 1 year. This study also demonstrated that the benefit was greatest to those patients with huge primary tumor (>10 cm in size). Although the benefits on overall survival has yet to be shown, as well as a number of unresolved issues such as cost-effectiveness and acquired drug resistance to tyrosine kinase inhibitors after prolonged use, these recent data shed lights on the potential adjuvant therapeutic role of tyrosine kinase inhibitors.

In this journal, Zeina AR, et al reported a case of fulminant hepatic failure due to metastatic GIST, which developed shortly after radical resection of the huge primary gastric tumor. The patient succumbed soon after the diagnosis was made. This patient with huge primary tumor and high mitotic figure represented the typical high risk patient for post-operative recurrence. The potential life-saving adjuvant imatinib therapy should be seriously considered in this group of patient, in the lights of recent important study findings.

Disclosure

The author reports no conflicts of interest.

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