RESEARCH ARTICLE

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Long-term Results of Adjuvant Imatinib Treatment for Localized Gastrointestinal Stromal Tumors after Surgery

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Abstract

Objective: Despite the development of two significant classifications for recurrence risk evaluation among patients engaged with gastrointestinal stromal tumor and corresponding treatment criteria, recurrence happens in a number of the patients who were once classified as ineligible for treatment and hence removed from treatment program. As such, the aim of the present study is to increase the number of patients recognized as eligible for treatment, so as to further reduce recurrence rate of this disease. **Materials and Methods:** A total of 26 patients from Ilam, Kermanshah, Lorestan, Kurdistan, and some parts of Hamedan, entered this study from 2006 until 2016. The western provinces included have similar socioeconomical conditions. Inclusion criteria were operable tumors confirmed radiologically with a gross size larger than 3 centimeters regardless of the mitosis rate in microscopic power fields, tumor location, or presence of peritoneal involvement during the surgery. Imatinib capsules were administered daily at 400 mg for 3 years. The patients were followed up every 3 months by radiology, ultrasonography, biochemical assessment, and clinical examination. **Results and Conclusions:** The overall survival after 10-years follow up was 100%, while 5-year survival without relapse was 95%. Mean overall survival was 106 months, and only one patient who had limited peritoneal involvement experienced relapse and he is still alive after 2 years. The drug was well tolerated and no significant side effects were observed.

Keywords: GIST- imatinib- target therapy

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Introduction

GIST is among common sarcomas. GISTs comprise less than 1% of all tumours developed in the gastrointestinal tract. Its annual prevalence has been estimated at about 10-20 cases per one million people (Judson and Demetri, 2007). Annual prevalence in US is almost 4,000 people (Corless and Heinrich, 2008). In the United States, 3,300 to 6,000 new cases of the disease are diagnosed each year. GIST originates from stomach, intestine, peritoneum, and rarely colorectal or other extraintestinal regions in the abdomen (Corless and Heinrich, 2004). Although this cancer is relatively rare in alimentary tract, it is the most prevalent sarcoma in this system. GIST occurs with similar prevalence in men and women and equally distributed across all geographic and ethnic groups, some studies are indicative of higher prevalence in men. (Miettinen et al., 2005; Miettinen and Lasota, 2006). Most patients present between the ages of 50 and 80 but the average age at the time of diagnosis is about 60 years (Nowain et al., 2005). Regarding the prevalence of involved regions, GIST is observed in stomach (40-70%), small intestine (20-40%), and colorectal (5-15%) and esophagus (≤1%). (Joensuu, 2006; Edge, 2010; Joensuu and DeMatteo, 2012). The most common metastatic regions are in peritoneum and liver. Surgery is the standard treatment for localized cases, and GIST patients need to have complete resection with surgery if possible (Casali et al., 2009). Most tumors do not show symptoms until they get large enough. These tumors may be discovered accidentally and not have clinical signs. These tumors might cause hemorrhage in alimentary tract and lead into melena and hematomesis (Miettinen and Lasota, 2006). Prolonged hemorrhages result in anemia in the person (Demetri et al., 2011). These tumors may cause obstruction, pain and discomfort in abdomen, feel of abdominal mass, nausea, vomit, loss of appetite, and weight loss (Miettinen and Lasota 2006; Demetri et al., 2011). The most common identified mutant genes in this disease include kit (90-95%), PDGF (10-15%), and CD34 (60-70%) and Constitutive activation of either of these receptor tyrosine kinases plays a central role in the pathogenesis of GIST(Heinrich et al., 2003; Joensuu, 2006; Corless and Heinrich, 2008), against which the drugs for treating this cancer are used (Heinrich et al., 2003; Joensuu, 2006; Corless and Heinrich, 2008). Historically, 50% of the patients die because of relapse despite complete resection of the gross tumor (DeMatteo, 2000). 35% of the patients with resected primary tumor

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experience relapse during the first 5 years and those in high risk group might have relapse sooner (DeMatteo, 2000; Pierie, 2001; Roberts and Eisenberg, 2002) . Relapse risk evaluation is based on mitosis rate, tumor place, tumor size, and peritoneal involvement (Eisenberg and Judson, 2004; Miettinen et al., 2005; Dematteo et al., 2008). In metastatic tumor cases, liver and retroperitoneum are typically involved. The 5-year overall survival specific to the disease is 28-60% among the patients with malignant GIST, and has been reported as 10-30% in metastatic or recurrent cases in some studies (DeMatteo et al., 2000; Crosby et al., 2001). In some cases, the disease relapses with delay after 5 years. Not all GIST patients may require treatment. Chemotherapy is not used in treatment due to lack of effect and target therapy is used in this disease for advanced or metastatic cases or in adjuvant cases after the surgery if there is a risk for relapse. Currently, the 3-year treatment with dose of 400 mg/day is considered as standard adjuvant therapy for patients with risk of relapse after surgery. Imatinib, an inhibitor specific for kit and PDGF is utilized for treating this disease (Ronald et al., 2013). Practically, most of the patients with GIST tumor express kit protein in IHC staining and 60-70% of the cases are also positive for CD34. Mutation in kit gene results in activation of intracellular signals cascades and cellular proliferation. Kit mutations are mostly located in 11 and 9 exons (Ronald et al., 2013).Treatment with Imatinib has well been tolerated in most studies. Side-effects are weak. The most common side effects include edema, nausea, diarrhea, musculoskeletal pain, tiredness, rush, headache, stomachache. Treatment in adjuvant cases is still a real challenge for GIST patients and strong criteria that can more accurately identify the patients with the risk of relapse have not yet been proved (Gold et al., 2009; Joensuu et al., 2015). So that evaluation of malignancy potential for primary GIST is still difficult, since malignancy potential is still unclear even in lesions smaller than 2 centimeters. Currently, there are two classifications for evaluation of relapse risk in patients with GIST as follow: The Armed Forces Institute of Pathology (AFIP) Miettinen Criteria and Lasota, the Modified National Institute of Health (NIH) Joensuu Criteria. In the criteria of Modified NIH Joensuu Criteria, tumor rupture is included in the criteria as a bad prognostic factor. In these classifications, the patients are categorized into groups with very low risk, low risk, moderate risk, and high risk. Mitosis rate, tumor size, tumor location, and peritoneal involvement rate are used to assess the risk in these classifications. 1. Tumor size larger than 10 centimeters, 2. Limited peritoneal involvement and perforation, 3. More than 5 mitosis in each microscopic field with spontaneous size of over 5 centimeters, are current criteria for high risk and treatment start. In trial of Scandinavia sarcoma group and German work group, some changes have been made in criteria of adjuvant therapy. Tumor size is perhaps the most reliable factor. Our study has been an open-label study, in which tumor size larger than 3 centimeters has been considered for beginning the adjuvant treatment, and it has been conducted to examine the influence and safety of Imatinib drug in these patients. This drug has been administrated for 3 years with the dose of 400 mg/day. We guess that Imatinib prolongs the overall survival of these patients following the resection of primary localized tumor. Regarding the low prevalence of this disease, undertaking a double-blind study was not feasible, so that the studied patients were directly headed into an open-label single-arm study.

Materials and Methods

Patients from western part of the country entered the study since 2006 until 2016. The term for entering the study was that the patient radiologically had the indication for complete gross resection of localized tumor, and GIST diagnosis was proved histologically by staining. Tumor size must be over 3 centimeters after the surgery. This size criterion is independent from presence or lack of over 5 mitosis, lesion location, visceral rupture, and limited involvement of peritoneum. Age of over 16 years, adequate end organ function, defined as the following: as total bilirubin $<1.5 \times$ ULN (upper limit of normal), serum AST (SGOT) and ALT (SGPT) $<2.5 \times$ UNL, creatinine $<1.5 \times$ ULN, ANC (neutrophil count) $>1.5 \times 10^9$/L, platelets $>100 \times 10^9$/Land ECOG performance status <2 were other criteria for inclusion in the study. Women or men in fertility age who had agreed to enter the study had to have suitable birth control and were not allowed to get pregnant for 3 months after drug cease. They must not have had lesions indicative of metastasis in lungs, abdomen, and pelvis CT-scan. Biochemical profile of the patients was evaluated. There was no patient following other procedures, so that no standard protocol other than that of our study existed at the center where the present research was conducted. Drug with the dose of 400 mg was administered for 36 months. Patients were visited each three months on the first 2 years, then each 6 months for 5 years, during which they were examined and the biochemical profiles were assessed. Abdominal and pelvic CT-scan and simple thoracic radiograph were performed each 6 months. In case of toxicity, drug dose was adjusted. Exclusion criteria included: inoperable GIST, metastatic GIST, recurrent GIST, other malignancy evidence, cardiac disease, lactation, uncontrollable diabetes, chronic renal failure, uncontrolled active infection, chronic hepatic disease, AIDS, and spontaneous usage of Warfarin and Acetaminophen unless these drugs were replaced.

Results

Patients entered the study successively since 2006 in a 10-year period. 50% of the patients were women and 50% were men. Regarding the involvement location, the most common organ was stomach (59.1%), then small intestine (18.2%), peritoneum (13.6%), and pancreas (4.5%). Considering the mitosis rate, 72.7% (16 patients) of the patients had mitosis rate of less than 5 in each microscopic field, and mitosis rate was more than 5 in 27.5% (6 patients) of the patients. 90% of the patients had complete excision with negative margin and 10% (1 patients) of the patients were not negative-margin in pathology report. Patient with negative margin is still in remission and lacks relapse. 90.9% of the patients were

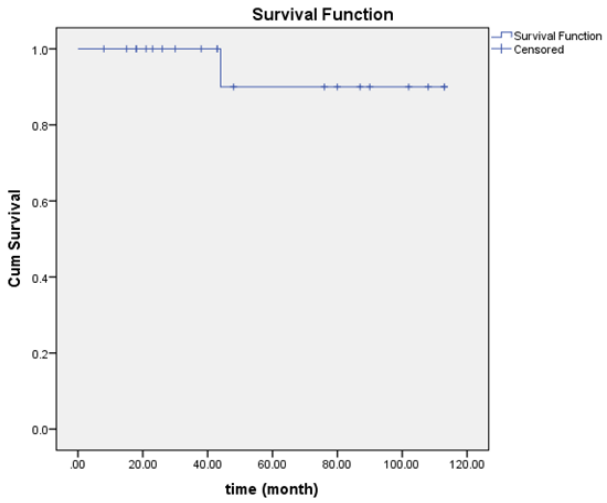

Figure 1. Means of Overall Survival Time for Our Patients

kit-positive and 9.1% were kit-negative. The mean of survival for patients was 106 months (Figure 1). The interesting point in this study was that, all of the operable patients were recognized as eligible (in terms of tumor size) for entering the study and beginning treatment following their surgery, except for one patient who had received neoadjuvant therapy.Adjuvant therapy was well tolerated. Most of the side effects were slight to moderate, and no side effect had resulted in ceasing the drug. Slight lowering of the dose was just done in some cases, and it was returned to the previous dose after remission. Some side effects which occurred in our patients could be mentioned as follow: superficial periorbital or lower limbs edema, nausea, grade 1 or 2 diarrhea, rush, tiredness, myalgia and arthralgia, stomachache, dermatitis. Superficial edema of periorbital region or lower limbs was managed using diuretics and other supportive interventions and the drug dose was lowered. Other side effects were slight and supportive interventions were just performed. The patient who was subjected to neoadjuvant therapy was indeed the one with well-developed GIST in his stomach. He exhibited very dramatic responses to the treatment based on the results of radiology and endoscopy analysis, but, unfortunately, refused to undergo a surgery. After two years of the beginning of the treatment with imatinib, he had the disease recurred. As of current, he undergoes treatment with Nexavar.

Discussion

The main treatment for GIST tumor is surgery, but relapse occurs in some of the patients after surgery, therefore regarding the presence of malignancy potential in this tumor, adjuvant therapy is recommended for some of these patients. Relapse risk estimation after resection of a primary GIST tumor is an important issue, based on which we choose those patients who probably take benefit from adjuvant therapy. Nonetheless, there is not a general agreement on risk criteria for relapse. In most studies, adjuvant therapy has been reserved for those patients who have estimated relapse risk of 30-50%. Large size, high mitosis rate in each microscopic field, locations other than stomach, ruptured tumor, and male sex are all bad prognostic factors. There is a nonlinear relationship between tumor size and mitosis rate, in one hand, and recurrence rate, on the other hand, and these factors increase the recurrence risk independently of one another, even though their combination (i.e. large tumor size together with high mitosis rate) further increases the recurrence rate(Dematteo et al., 2008). Other factors such as spontaneous disease, age, performance status, and mutant genes condition all affect the doctor's decision making for adjuvant treatment. Mutation of exon 11 could be mentioned among the mutations for which adjuvant therapy might be recommended (Fletcher et al., 2002; B. Kang et al., 2009). In cases with mutation in PDGFRA 842V gene, adjuvant therapy could not be recommended (Corless et al., 2014). Treatment is recommended for other mutations. Models and classification schemas of risk are not suitably predictive of relapse-free survival and do not accurately determine the high-risk patients. Thus, other trials have been performed to include more patients with GIST in adjuvant therapy program, and those who have not been candidate for adjuvant treatment according to the previous risk categorizing models which mostly had been based on tumor size. Trial of ACOSOG Z9001could be mentioned among trials done based on the size (Dematteo et al., 2009). In their study, tumor size larger than 3 centimeters was considered for beginning the adjuvant treatment. Tumors of 3 centimeters or larger size were considered in the probable relapse risk in that trial and adjuvant therapy was done. In the ACOSOG Z9001 study the patients were divided into two groups, one receiving placebo and the other receiving Imatinib. Since less patients experienced relapse in the group that had received treatment, this trial was ceased at the beginning, and all the placebo patients went under treatment with Imatinib, too. Relapse rate was at minimum during the first year, but it increased after 18 months. It has been mentioned in the first report of this trial that the drug has been well tolerated and has not had any significant side effect. Although no difference was seen between the two groups regarding the overall survival, it has been noted that it might be due to short follow up, limited number of relapsed patients, crossover of patients in placebo group with Imatinib receiving group after more relapses in patients from placebo group, and high grade of Imatinib impact in relapsed patients. In the one-year follow up, relapse-free survival was 98% in Imatinib group and 83% in placebo group. Relapse-free survival was better in the Imatinib receiving group in that study. In ACOSOG Z9001 study, drug effectiveness has been similar in all high risk groups including tumor size, tumor location, and mitosis rate. This trial has concluded that Imatinib might simply hinder the relapse. The main question has been whether improved relapse-free survival may lead into enhanced overall survival, for the answer of which Intergroup EORTC 62024 trial was initiated (according to the 2002 NIH classification and including tumor rupture or intraoperative tumor spillage) (Casali et al., 2015). In that trial, 908 patients with moderate to high risk were

randomly divided into two groups of drug and control. In a follow up of 4.7 years in average from initiation of the treatment until death or starting another drug other than Imatinib, 5-year survival was 87% in Imatinib group and 84% in placebo group, which is indicative of the impact of using adjuvant treatment in GIST. In 2008, FDA approved Imatinib as adjuvant for resected primary tumors of over 3 centimeters which was updated in 2012.

In our study, after an 11-year follow up with an average of 6 years, 100% of the patients were alive and only one patient with peritoneal involvement experienced relapse 1.5 years after ceasing the 3-year treatment who is currently under treatment and has not died yet. Mean of overall survival was 106 months. Although, our criterion for entering the study was tumors larger than 3 centimeters, our patients had large tumor size, and before diagnosis their tumors had significantly grown, so that 38.4% of the patients had tumors larger than 10 centimeters. More than 15 patients in our study had tumors larger than 5 centimeters. In comparison with the historical group, the relapse rate was too low and just one patient experienced relapse in our study and patients' survival has been remarkable. No significant side effects have been caused by Imatinib and drug toxicity was acceptable, and no ¾ grade hematologic and non-hematologic adverse effects were observed in current study. Therefore, in cases of tumors larger than 3 centimeters, we recommend Imatinib treatment regardless of mitosis rate and tumor location. However, more extensive studies are required. We also recommend adding mutant gene to the prognostic factors in guidelines for adjuvant therapy, since prognosis of mutation in exon 9 is worse than exon 11. Moreover, it should be addressed that tumors with mutation in PDGF gene are less probable to ameliorate.

In conclusion, GIST tumors larger than 3 centimeters could independently make these patients candidates for adjuvant treatment regardless of the tumor location and mitosis rate, and this treatment has reduced disease relapse in long-term follow up compared to the control group.

Conflict of interest

The authors have declared no potential conflicts of interest.

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