Risk Group Stratification of Patients with Gastrointestinal Stromal Tumors to Determine Expediency and Duration of Adjuvant Therapy

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ABSTRACT

Experience of adjuvant therapy of patients with gastrointestinal stromal tumors (GISTs) has demonstrated high efficacy allowing almost two-fold increase of patients' recurrence-free survival. Currently, low risk patients after radical surgical treatment are closely followed up; moderate risk GIST patients are recommended adjuvant therapy with Imatinib for 1 year whereas those of high risk – for 3 years. This article presents the review of significant predictors, analysis of which shall let a clinical oncologist stratify patients into risk groups most precisely thus improving the efficacy of target therapy.

Keywords: gastrointestinal stromal tumors, adjuvant therapy, risk group, Imatinib

New discoveries in the area of molecular biology, immunohistochemical assay (IHA), studying prognostically significant morphological features of the malignancies' structure as well as advances of target therapy allowed developing and introducing new approaches to differential diagnosis and treatment of patients with mesenchymal tumors of the gastrointestinal tract to clinical practice.

For the first time, gastrointestinal stromal tumors (GISTs) were segregated as a separate disease only in 1983 [24]. Until that time, given neoplasms fall into the category of 'other' types of sarcomas.

GISTs belong to rare tumors accounting for 0.1- 3% of all GI malignancies; however, their proportion among all sarcomas of the GI tract is as high as 80% [29,40]. Besides, many GISTs remain unidentified: 20% of tumors present themselves the endoscopic findings or are accidentally encountered on radiological examination of the abdominal cavity; microscopic GISTs are found in 35 out of 100 patients operated on for stomach cancer; 10 unrecognized GISTs are found per 1,000 autopsies [32,20].

In a number of clinical trials, correlation between the efficacy of surgical treatment of GIST patients and degree of local spread of the disease/radicalism of a surgical intervention has been shown. Thus, the recurrence rate is equal to 35% for the localized lesion and amounting to 90% for the locally disseminated process. On an average, the 5 year-survival of patients after surgical treatment varies from 35% to 65%. Recurrences occur within two years in 80% of observations [9,34]. In case of recurrence or diagnosis of the primary non-operable/disseminated process, median survival is 10-20 months [10,36]. As a rule, surgical removal of the recurrent lesions does not lead to improved prognosis [33].

Experience of using systemic chemotherapy for treating this group of tumors has demonstrated lack of satisfactory outcomes. Most often, Doxorubicin and Dacarbazine were used. However, neither mono-chemotherapy nor most commonly used combination MAID has not been efficacious: by different authors, the response rate varied from 0% to 27% whereas overall median survival was 14-18 months [3, 35, 45]

Discovery of the major pathogenetic mechanism responsible for GIST – hyperactivation of the c-KIT receptor [17,21] – as well as results of preclinical trials of the STI-571 drug laid the foundation for assessing the effectiveness of the targeted drug Imatinib and its incorporation into broad clinical practice for treating GIST patients, which permitted twofold extension of life expectancy of this patient population [43,44].

Within the framework of a large randomized double-blinded clinical trial ACOSOG Z9001 carried out in the US that enrolled 713 patients with localized types of GISTs from 230 hospitals in the US and Canada, the efficacy of 1-year adjuvant therapy after radical surgical treatment of this patient cohort has been proven [5]. Exclusion criteria were as follows: patient age older than 18 years, tumor over 3 cm in diameter, CD117-positive tumors. Patients were divided to two groups: the first group (n=359) has been prescribed Imatinib 400 mg/day during one year; the second group (n=354) has been given placebo. It was found that adjuvant therapy with Imatinib has contributed to the improvement of recurrence-free survival indicators from 83% in the control group to 97% in the group of postoperative treatment [5]. Two-year recurrence-free survival of high-risk patients with localized GISTs turned out to be almost two times higher with Imatinib versus placebo: 77% and 41%, respectively (Table 1) [5].

Table 1

The 2-year recurrence-free survival of GIST patients by degree of risk (phase III of clinical trial Z9001)

Degree of risk	Group of Imatinib adjuvant therapy	Control group (placebo)	*p*
Low	98%	98%	0.92
Moderate	98%	76%	0.05
High	77%	41%	<0.0001

Such a significant difference in recurrence-free survival prompted a decision made by protocol's developers on unblinding study's results, and patients from the placebo group were offered treatment with Imatinib.

Results of the clinical trial ACOSOG Z9001 served as a basis for approving Imatinib as a drug for 1-year adjuvant therapy of c-kit+ GISTs in the US in 2008 and in Europe and Russia in 2009.

Similar results were obtained in a number of other clinical trials. In particular, Zhan W.H. et al. studied the efficacy of Imatinib adjuvant therapy in GIST patients at high risk of recurrence (tumor size over 5 cm and presence of 5 or more mitoses in 50 fields of vision at 400x magnification) [46]. Fifty seven patients with high risk GISTs were enrolled in this study. From 2004 to 2005, all patients underwent radical surgical treatment for the primary tumor followed by adjuvant therapy with Imatinib 400 mg/day. With median follow-up of 12 months, metastases occurred only in 2 (3.5%) patients. The median recurrence-free period was 12.8 months [46].

Within the framework of the clinical trial EORTC 62024, results of which were presented at the 2013 ASCO meeting, the efficacy of Imatinib adjuvant therapy versus surgical treatment with subsequent dynamic follow-up was studied in patients with high and moderate GIST risk. 908 GIST patients enrolled in the study were divided to two groups of 454 individuals each: in the first group, adjuvant therapy has been given for two years; in the second group, targeted therapy after surgery has not been given. By results of this trial, the 3-year recurrence-free survival in the adjuvant treatment group amounted to 84%; in the dynamic follow-up group – 66%. Upon completion of the program, investigators came to conclusion that Imatinib adjuvant therapy in populations of patients with moderate and high risk GISTs should have been given for more than 1 year [13].

In the Scandinavian multicenter prospective randomized clinical trial SSG XVIII/AIO, 2 options of duration of Imatinib adjuvant therapy of 400 high risk GIST patients were compared. Follow-up lasted for a median of 54 months. In this trial, a significant advantage of 3-year Imatinib adjuvant therapy has been found. 5-year recurrence-free survival in the group receiving treatment for three years was 66% as opposed to 48% in the group of 1-year targeted therapy. The 3-year recurrence-free survival in the group of 3-year therapy was 92% compared to 82% in the group of 1-year therapy. Tolerability of Imatinib therapy, in general, was good. A proportion of patients who quit taking Imatinib during the period of their participation in the study for any reasons excluding GIST recurrence was 26% in the 36 month adjuvant therapy group and 13% – in the group receiving Imatinib for 12 months [18].

Based on this trial, in 2012 changes have been made to the European Society for Medical Oncology (ESMO) guidelines: for patients with high risk GISTs after a radical surgical operation, Imatinib adjuvant therapy is recommended for 3 years [12].

In accordance with the International Classification of Diseases for Oncology, there are benign, dubious prognosis and malignant GISTs. There is an opinion concerning both potentially malignant nature of all GISTs and benign nature of tumors smaller than 2 cm and those with minimal mitotic activity. At the same time, cases of recurrences and metastases of any size GISTs are described [20].

At present, making diagnosis of GIST is based on morphological and immunohistochemical data. Main histological types of GIST are spindle cell (70%), epithelioid cell (20%) and mixed (10%). In the study carried out by Singler S. et al., it was found that the 5-year recurrence-free survival in the setting of spindle cell GIST amounted to 61%, epithelioid – 33%, and mixed – 23% (p=0.002) [41].

The Joint Working Group of the National Institutes of Health (NIH) established for studying GIST recommends using the system of determining ‘risk of aggressiveness’ that takes into consideration just tumor size and a number of mitoses in 50 representative fields of vision at x400 magnification (Table 2) [27].

Table 2.

Assessment of the GIST malignant potential

Risk level	Tumor size	Mitotic index
High	does not matter	≥ 10/50
	≥ 10 cm	does not matter
	≥ 5 cm	≥ 5/50
Medium	5-10 cm	≤ 5/50
	≤ 5 cm	6-10/50
Low	2-5 cm	≤ 5/50
Extremely low	≤ 2 cm	≤ 5/50

While differentiating GISTs by degree of malignancy, some authors rely upon the system of criteria suggested by the French National Federation of Cancer Centers that was developed for histological grading of sarcomas along with assessment of the severity of cell polymorphism, indicators of tumor cellularity, presence of mucosal invasion and sites of necrosis [15].

At the same time, guidelines of the European Society for Medical Oncology (ESMO) and the US National Comprehensive Cancer Network (NCCN) reflect the fact that localization of the primary tumor possesses even more significant prognostic value (Table 3) [8,11].

Table 3.

Risk of GIST progression by mitotic index, tumor size and localization

Mitotic Index (number of mitoses in 50 fields of vision)	Tumor size (cm)	Risk of disease recurrence (%)			
		Stomach	Duodenum	Small intestine	Rectum
≤ 5	≤2	0	0	0	0
	>2,≤5	1.9	8.3	4.3	8.5
	>5, ≤ 10	3.6	*	24	*
	>10	10	34	52	57
>5	≤2	*	*	*	54
	>2, ≤ 5	16	50	73	52
	>5, ≤ 10	55	*	85	*
	>10	86	86	90	71

Note: *No accurate data is available

Significance of the primary tumor as a prognostic factor has been also demonstrated in papers by M. Miettinen. This author came to conclusion that patients with the primary tumor in their gut would have worse prognosis [27].

In 2008 in order to clarify indications for adjuvant therapy, H. Joensuu has made a suggestion to modify the classification of risk groups with consideration of primary tumor's localization (Table 4) [19].

Table 4.

Risk of GIST progression

Risk	Tumor size, cm	Mitotic index	Tumor localization
Very low	<2	≤5	Any
Low	2.1-5.0	≤5	Any
Intermediate	2.1-5.0 <5 5.1-10.0	>5 6-10 ≤5	Stomach Any Stomach
High	Any >10 Any >5.0 2.1-5.0 5.1-10.0	Any Any >10 >5 >5 ≤5	Tumor rupture Any Any Any Outside the stomach Outside the stomach

Likelihood of recurrence in 2 and 6 years after radical surgical treatment may be calculated with the use of nomograms presented in the paper by J. S. Gold: risk assessment is done by tumor size, its localization and mitotic index [14].

Besides, the ESMO guidelines recognize the importance of tumor capsule's rupture (both spontaneous and due to surgical resection) as an unfavorable prognostic factor given accompanying contamination of the peritoneum [11].

High Ki-67 proliferation index (over 10% of nuclei expressing Ki-67) and loss of expression of neurogenic and smooth muscle cell differentiation's markers by the tumor cells are also currently perceived as objective signs of unfavorable prognosis [38].

The need for accurate stratification of recurrence risk became especially pressing after the introduction of Imatinib into common clinical practice as a drug for adjuvant therapy. According to modern data, genotype of the primary GIST determining its response to Imatinib therapy is the most important predictor (Table 5) [25,26,30,39].

Table 5.

Clinical significance of various mutations of the c-kit and PDGFRa genes

Mutation site	% of all mutations	Clinical significance
c-kit, exon 11	5-15	All localizations, good response to Imatinib
c-kit, exon 9	60-70	Many tumors of the small intestine. Less sensitivity compared to exon 11 mutations; escalating the daily dose of Imatinib up to 800 mg is effective
c-kit, exon 13	1	Imatinib is efficacious
c-kit, exon 17	1	Imatinib is efficacious
PDGFRa, exon 12	1	Tumors are localized in the stomach; Imatinib is efficacious
PDGFRa, exon 14	Less than 1	Extremely rare cases
PDGFRa, exon 18	5	Stomach tumors are more common, variant D842 is sensitive to Imatinib
Wild type	10-15	Only 40% of tumors respond to Imatinib; pronounced primary resistance
GIST in children	3	Mutations in the c-kit and PDGFRa genes are absent
Carney triad	Less than 1	Mutations in the c-kit and PDGFRa genes are absent
GIST in a combination with neurofibromatosis	Less than 1	Mutations are rather absent; possible mutation in the NF1 gene

It's noteworthy that in contemporary literature controversial opinions on prognostic value of KIT exon 11 mutations are reflected. Some authors link this type of mutation to high degree of tumor's malignancy [22,42]. Others believe that KIT exon 11 mutations are frequently seen in benign GISTs [1]. However, stromal tumors of the GI tract with the KIT exon 11 mutation are the most sensitive to Imatinib: complete regression of the tumor is noted in 6% of cases; partial regression – in 61%; process stabilization – in 25% and progression – in 3% of cases [4, 37].

The therapeutic effect of Imatinib in patients with KIT exon 9 mutations is not that good: complete regression of the tumor is noted in 5% of cases; partial regression – in 29%; process

stabilization – in 47%; disease progression – in 17% of cases [4, 37]. Efficacy of this therapy is achieved through escalating daily doses of the drug up to 800 mg. It should be noted that, by literature data, there are no significant differences in survival between patients with stromal tumors with deletions in exons 9 and 11 of the KIT [28, 29, 3].

GISTs with the mutation in exon 13 of the KIT are associated with more aggressive course of the disease as opposed to GISTs with the mutation in exon 17 in patients with stromal tumors of the stomach. At the same time, clinical course of stromal tumors of the small intestine with mutations in exons 13 and 17 of the KIT gene is not different from that of other stromal tumors of the same localization [2].

GISTs with PDGFRa mutations, in general, are associated with low mitotic activity and more favorable clinical course. Most frequently, these tumors are localized in the stomach [6, 7].

Primary resistance to Imatinib is observed in patients with mutations in exon 17 of the KIT and exon 18 of the PDGFRa [4, 37].

In small groups of GIST patients, other clinical and pathological prognostically important factors have also been demonstrated. Thus, in the paper by Martin J. et al., high cellularity has been described as an independent factor of low 5-year recurrence-free survival compared to moderate or low cellularity tumors [23]. Hassan I. et al. have demonstrated in their works that prognosis in patients with clinical symptoms of the disease upon diagnosis was worse than that in asymptomatic patients [16].

By now, prognostic value of many other biological and histopathological GIST factors such as DNA ploidy, tumor necrosis, expression of CD44, insulin-like growth factor-1 & 2, retinoblastoma protein, degree of cellular atypia, expression of S-100, telomerase activity, microvascular density and lack of KIT gene expression is considered. However, due to the small size of samples and retrospective nature of these studies it's difficult to identify the impact of single clinical and pathological factors on disease course's prognosis. Besides, these indicators in the majority of observations were associated with other high risk factors (large tumor size or big number of mitoses), which further decreased independence of their prognostic value.

For intermediate risk of GIST progression, approaches to adjuvant therapy are not yet defined. Research in this area continues.

To date, importance of identifying risk factors of GIST progression for a prognostic purpose does not cause any doubts. A hefty number of clinical trials devoted to studying these signs have been conducted. Summarizing the results yielded, the largest oncology societies worldwide came to conclusion that in order to increase the duration of efficacious therapy and,

as a consequence, improve GIST patients' survival, one would need to consider a broad range of factors permitting the assessment of tumor aggressiveness.

Risk stratification is a matter of paramount importance for selecting GIST patients who are indicated adjuvant therapy with Imatinib. Assessing risk of disease progression based on the analysis of such prognostic factors as neoplasm's size, its localization, mitotic rate, rupture of the tumor capsule and mutation site shall allow more thorough dividing patients into risk groups entailing the improved recurrence-free and overall survival of GIST patients.

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