Prognostic Markers in Gastrointestinal Stromal Tumors – We Are Not There Yet

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Gastrointestinal stromal tumors (GISTs) comprise the largest subset of mesenchymal tumors of the digestive tract. It has been suggested that these tumors originate from the interstitial cells of Cajal or from their stem cell-like precursors [1]. Most GISTs have an activating mutation in the *c-kit* protooncogene that leads to constitutive expression of Kit protein, a tyrosine kinase specific to the stem cell factor [2]. Therefore, in the context of appropriate morphology, these tumors are best defined by Kit (CD-117)-positive immunostaining. Recently, an activating mutation of platelet-derived growth factor receptor- α (PDGFR α) was identified to comprise ~5% of GISTs [3, 4]. GISTs have a wide range of biological behaviors, including benign, borderline and malignant variants. Approximately 20–25% of gastric and 40–50% of small intestinal GISTs are clinically malignant [5]. The treatment of GIST is complete excision when possible, and treatment with Kit/PDGFR α tyrosine kinase inhibitors, such as imatinib, when the tumor is unresectable or in the metastatic setting. The majority of patients can achieve complete or partial remission. Long-term success is limited by the development of imatinib resistance, usually based on secondary mutations in the Kit or PDGFR α tyrosine kinase domains [6, 7].

The most widely examined criteria for evaluating biological potential of GISTs are tumor size and mitotic activity [8, 9]. Unfortunately, these indices do not guarantee a benign clinical course, as small GISTs with a low mitotic

index have been known to metastasize. This has prompted the development of guidelines for defining risk of aggressive behavior rather than classifying lesions as either benign or malignant [10]. These guidelines, which were developed during a NIH consensus conference in 2001, are based on the idea that all GISTs have some potential for aggressive clinical behavior. Other pathological features of GISTs, in addition to mitotic index and tumor size, such as cellularity, mucosal invasion and ulceration, were also evaluated for prognostic significance, but have not gained wide acceptance [11]. Kit mutation status has also been evaluated in terms of prognosis. However, since approximately 90% of GISTs contain either Kit or PDGFR α mutations, the presence or absence of a mutation does not, by itself, distinguish between benign and malignant GISTs [12, 13]. Preliminary studies indicate that accumulation of secondary cytogenetic abnormalities/molecular alterations [12], Ki-67 proliferative index and telomerase activity are associated with clinically aggressive behavior [14]. Aberration of the cell cycle regulators is a frequent finding and may be a contributing factor in the pathogenesis of GIST. Indeed, malignant GISTs are more likely to be associated with a positive E2F1 and p53 phenotype and a negative p16 and p27^{kip1} phenotype [15–17]. For p27^{kip1}, a member of the Cip/Kip family, a tumor suppressor role was demonstrated in mice, and a decrease or loss of the p27^{kip1} protein was found to be a predictor of poor prognosis in many human cancers, including gas-

gastrointestinal malignancies [18, 19]. An inverse correlation was demonstrated for different tumors between p27 expression and tumor grade, stage and survival [20]. Several studies demonstrated a negative correlation between p27 and Ki-67 proliferation index supporting the role of p27 as a prognostic marker GISTs [16, 21, 22], on the other hand a more recent study could not confirm these findings [23].

In this issue of *Digestion*, Shirin et al. [24] examined in 36 patients with surgically resected GISTs, whether p27 may predict the malignant potential of the tumor. The patients were classified into benign or malignant GISTs. Clinically, 25 patients (~70%) had benign GIST with no involvement of regional lymph nodes or distant metastases. Using immunohistochemistry, tumor specimens were stained for p27 and the proliferation marker, Ki-67. The authors observed a significant difference between low- and high-risk GIST groups for Ki-67 expression, while no difference was identified for p27 expression, tumor size or predominant cell type (i.e., spindle or epithelioid). Ten patients died due to causes unrelated to their GISTs: 5 died perioperatively and another 5 patients died during follow-up from other causes. Only 1 patient died because of recurrent GIST. With only one GIST-related death (an exceptionally favorable prognosis for GIST patients with a 10-year follow-up), it is not possible

to conclude, from this study, any correlation between p27 expression and survival. Therefore, this study does not clearly exclude an association between p27 expression and patients' prognosis, but rules out a correlation with the stage of the tumor during surgery.

Although in this study the percentage of patients with low-risk GISTs is small (i.e., 16%), which may hamper the recognition of statistically significant differences in the expression of p27 between the two groups, a significant difference could be seen in the Ki-67 expression between the low- and high-risk groups. Unexpectedly, in this study, a trend for higher p27 expression was found in the more advanced tumors (although not statistically significant), in contrast to previous studies where low p27 expression was associated with an unfavorable prognosis [16, 20–22].

In summary, this study suggests that p27 expression cannot serve as a predictor for the aggressiveness of GIST, and therefore cannot predict prognosis or indications for further treatment after surgery. It should be emphasized, however, that since there was only 1 case that died as a result of his GIST, p27 expression cannot be used as a prognostic marker. Clearly, more research is necessary to elucidate new markers with a good correlation to prognosis that will aid in selecting those patients who will require additional therapy following surgical resection.

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