Evaluating and Reporting Gastrointestinal Stromal Tumors after Imatinib Mesylate Treatment

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Abstract: Malignant and advanced gastrointestinal stromal tumors (GIST) are currently treated with imatinib mesylate, an inhibitor of KIT and PDGFRA receptor tyrosine kinase. Pathologic evaluation of residual disease is the gold standard in these cases, as clinical and radiologic assessments of treatment response do not always correlate with the pathologic response. Phenotypic and genotypic changes may also occur which may have an impact on treatment decisions. This review will focus on the role of the pathologist in ordering appropriate testing for the primary tumor, the morphologic, phenotypic and genotypic changes seen following imatinib therapy in cases of advanced GIST, and essential components of the pathology reports.

Keywords: GIST, imatinib mesylate, gleevec.

INTRODUCTION

Gastrointestinal stromal tumor (GIST), the most common mesenchymal neoplasm of the gastrointestinal tract, is characterized by the expression of the tyrosine kinase receptor KIT [1, 2]. GISTs have many features in common with other spindle cell mesenchymal tumors of the gastrointestinal tract, and thus the pathologist plays a critical role in correctly distinguishing GISTs from morphologically similar tumors. The diagnosis depends on proper usage of appropriate immunohistochemical staining methods, which may be on occasion supplemented with genetic and molecular biology tests. Such testing is performed on both pre and post treatment specimens.

CD117, the immunohistochemical marker for KIT, is expressed in over 90% of tumors, and is now used routinely as a diagnostic marker [3]. Among the remaining KIT negative GISTs, up to 5% have an activating mutation in the PDGFRA gene, which has similar tyrosine kinase properties [3].

Imatinib mesylate (Gleevec, ST1571, Novartis Pharmaceuticals, Basel, Switzerland) the oral agent that inhibits KIT and PDGFRA receptor tyrosine kinase has shown to induce partial response or arrest the progression of the disease in over 80% of patients with metastatic or advanced unresectable tumors [1, 3].

Patients with no immunophenotypic evidence of a KIT or PDGFRA mutation may still be eligible for imatinib treatment; however, as KIT negative GISTs may contain imatinib-sensitive KIT or PDGFRA mutations at the genotypic level. Pathologists may be called upon to order genotypic analysis on the primary tumor in these cases [4].

Primary resistance to imatinib is seen in 15% of patients with GISTs, and the surgical specimens from such persons will show a correlating lack of histologic response [3, 5].

Mutational analysis has shown that different genotypic mutations correlate with treatment response, thus increasingly, physicians may request genotypic analysis of advanced GIST cases to aid treatment decisions [2, 4-7]. Mutational analysis is not typically indicated for localized KIT positive GISTs which are completely resectable by surgery alone; however, in cases where imatinib therapy may be employed, such as patients with advanced metastatic or recurrent disease, genotyping is recommended [4].

Though patients may show initial response on imatinib, many will eventually progress and require histopathologic examination and molecular analysis of the tumor to help explain the cessation of response. Many patients develop secondary resistance to imatinib, and frequently second site KIT mutations are seen in explanation to this response, giving a potential reason for genetic analysis in the post-treatment setting [3, 6].

Though surgery remains the mainstay of treatment, since the approval of imatinib, many patients are now receiving this treatment for advanced or metastatic GISTs. Numerous studies have shown increased survival after resection of GISTs, and often, imatinib treatment makes resection more feasible. In addition, recent studies show a beneficial role for adjuvant therapy with imatinib even for localized primary GISTs [8]. Therefore, pathologists will be called upon to examine more post-treatment specimens for evidence of residual disease, and to order appropriate tests.

SPECIMEN HANDLING

Clinical history and pathologic history is essential prior to evaluating a specimen. Particularly important in GIST cases is knowing the morphologic pattern and CD117 expression status of the original tumor, as these may change following treatment. Standard grossing protocols are...
adequate for sampling the original primary tumor site, as well as metastatic sites and lymph nodes. In large tumors, or in areas with no grossly visible tumor, numerous sections may have to be screened in order to detect residual viable tumor cells.

**THERAPY INDUCED MORPHOLOGIC CHANGES**

Since the first GIST cases were treated with imatinib in 2000, histologic findings status post treatment have been documented, though cases noting a complete pathologic response are rare [1, 9].

Histologic examination of resected treated GIST remains the most accurate way of documenting residual disease, as radiologic and clinical response rates have poor correlation with pathologic response rate. The use of PET, especially, is noted for its poor correlation to the histologic response [7, 10].

Histologic response tends to be heterogeneous [4], not only in the same resection specimen, but also within individual lesions in the specimen (Fig. 1). Residual tumor cells may be seen scattered in hyalinized interstitial tissue (Fig. 2) or in the form of small groups and even large nodules composed of densely packed cells [9].

![Fig. (1). Histologic response to imatinib therapy is often quite heterogeneous. At the upper left a large hypercellular tumor nodule is present, while the lower right area shows hyalinizing treatment effect with more dispersed tumor cells (HE X100).](image)

![Fig. (2). In one pattern of residual disease, tumor cells are often replaced by a hyalinizing process, with only scattered spindled tumor cells remaining (HE X100).](image)

The most frequent changes noted following treatment are hyalinization and scarring [1, 3-9]. Large portions of the tumor may be composed of hyalinized stroma containing no viable tumor cells (Figs. 3, 4). Additional treatment effects include myxoid degeneration, (Fig. 5), fibrosis, (Fig. 6), hemosiderin deposition, and infiltrates of inflammatory and foam cells (Fig. 7). Tumor necrosis may be found, but it is not a frequent finding (Fig. 8). Even in patients who show a good clinical response a complete pathologic response is unlikely.

![Fig. (3). Hyalinization is a frequent treatment effect. These images show hyalinization on the left, while on the right a hypercellular tumor nodule remains (HE X200).](image)

![Fig. (4). Beneath the relatively normal mucosa, only hyalinized tissue is found, with no residual disease present (HE X40).](image)

![Fig. (5). Another common treatment effect is myxoid degeneration of the tumor cells (HE X100).](image)
Fig. (6). This case shows minimal treatment effect in the form of fibrosis in the center of an otherwise hypercellular tumor (HE X40).

Fig. (7). Collections of foam cells may be seen following treatment (HE X100).

A proposed grading system to classify the histologic response includes the following four categories:

- Minimal (< 10% response)
- Low (10-50% response)
- Moderate (50-90% response)
- High (> 90% response)

This grading system has been primarily used in research applications, and is not a required element of the final pathology report. The pathologic changes suggesting a response to therapy, and the nature of specific histologic changes seen should be nevertheless documented [3].

Immunohistochemical staining for CD117 expression is useful for identifying residual GIST cells [7], especially in hyalinized areas, where single tumor cells can be difficult to detect (Figs. 9, 10). Treatment changes in metastatic sites and lymph nodes are similar to those seen in primary sites (Fig. 11).

Current therapy with imatinib mesylate has no adverse effects on adjacent normal tissues. Endothelial cells in the area of tumor have been reported as histologically normal following treatment, and no treatment effects were noted in the stromal or epithelial cells of the stomach and intestines [1].

Fig. (8). On the right tumor cells show myxoid degeneration, while on the left necrosis and hemorrhage can be seen (HE X200). Tumor necrosis is an uncommon response to imatinib treatment.

Fig. (9). In a largely hyalinized background, residual tumor cells may be difficult to distinguish from inflammatory cells or fibroblasts (HE X100).

Fig. (10). Immunohistochemical staining for CD117 expression is useful to identify residual GIST cells, especially in hyalinized areas, where single tumor cells can be difficult to detect (CD117 X100).
CD117 expression. CD34 immunoreactivity may also be lost, immunoreactivity, even if the primary tumor showed classic from patients on treatment can show complete loss of CD117 immunophenotypic changes as well [11]. GIST specimens Tumors may not only show morphologic changes, but genotypic level, the original KIT or PDGFRA mutations were retained in all cases, and did not show additional tumor, and the immunohistochemical stain for MIB-1 (Ki-67) is useful in evaluating post-treatment resection specimens [4, 7]. The degree of histologic response does not correlate with the duration of imatinib treatment, and the intensity of residual CD117 staining does not correlate with the overall response to treatment [7]. The comparison of pre-treatment and post-treatment specimens indicates that the latter could contain fewer mitoses, suggesting that the mitotic count could be used to assess the efficacy of treatment [5, 9]. The proliferative index, however, has not been shown to correlate with the degree of clinical or histologic response, the genotype, or the duration of treatment. Still, the mitotic count provides valuable data about the aggressive nature of the residual tumor, and the immunohistochemical stain for MIB-1 (Ki-67) is useful in evaluating post-treatment specimens [4, 7]. Recently five cases of heterologous rhabdomyosarcomatous differentiation in treated GIST have been reported [12]. In all cases the cells showing this unusual morphology were next to areas with classic GIST, indicating that they arose in response to treatment. CD117 and CD34 staining in these areas were negative or weak, and the rhabdomyosarcomatous areas showed gain of markers typically seen in malignant tumors of striated cells, such as desmin or MYF-4. At the genotypic level, the original KIT or PDGFRA mutations were retained in all cases, and did not show additional secondary KIT mutations [12].

THERAPY INDUCED PHENOTYPIC CHANGES

Tumors may not only show morphologic changes, but immunophenotypic changes as well [11]. GIST specimens from patients on treatment can show complete loss of CD117 immunoreactivity, even if the primary tumor showed classic CD117 expression. CD34 immunoreactivity may also be lost, and gain of expression of markers, such as desmin, may be seen. Desmin positivity as an indicator of smooth muscle differentiation has been noted in several cases following treatment. Ultrastructural changes consistent with smooth muscle features have been documented with electron microscopy, suggesting true smooth muscle differentiation in these cases. This indicates that a minority of treated GISTs might undergo transdifferentiation to a smooth muscle phenotype, giving another potential diagnostic pitfall of which pathologists must be aware [7].

The role of abnormalities of other genes such as p53 and BCL-2 in GIST remains uncertain. Agaram et al. [7] showed the presence of p53 gene alterations did not affect clinical or histologic response to imatinib, and BCL-2 positivity showed no correlation with histologic response or proliferative index. The use of these markers in a post treatment setting is still investigational and not necessary for routine reporting.

THERAPY INDUCED GENOTYPIC CHANGES

Even though the phenotypic immunohistochemical features of the original tumor, such as CD117 and/or CD34 can be lost during therapy, genetic studies show that the original KIT mutations are retained in the majority of treated tumors [11]. KIT mutational analysis may be useful in the setting of an unexpected immunohistochemical profile or histomorphologic changes that occur following treatment. KIT mutational analysis may also be requested by clinicians while investigating possible reasons for treatment failure or resistance.

CONCLUSION

Treatment of GISTs with imatinib and/or one of the newer tyrosine kinase receptor inhibitors results in a clinical and radiologic response which must be documented pathologically. Proper handling and reporting of these specimens will be key to patient management. Standard grossing protocols should be followed, morphologic changes and treatment effect should be documented, and an immunohistochemical panel including CD117, CD34 and MIB-1 should be performed on all post-treatment surgical specimens. Genetic mutational analysis is appropriate in cases which lose immunophenotypic expression of CD117, or to document possible secondary mutations in treatment-resistant cases.

ABBREVIATIONS

GIST = Gastrointestinal Stromal Tumor
PDGFRA = Platelet-Derived Growth Factor Receptor Alpha

REFERENCES

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