

Gastrointestinal stromal tumors and second primary malignancies before and after the introduction of imatinib mesylate

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Gastrointestinal stromal tumor (GIST) is the most common mesenchymal malignancy of the gastrointestinal tract. GISTs may coexist with different types of cancer, either synchronous or metachronous (1). Most GISTs develop in a sporadic fashion, but familial occurrence, such as neurofibromatosis and Carney-triad, has also been reported (2). The overall frequency of second tumors in different series varied from 4.5% to 33%. The most frequent types of GIST-associated cancers were gastrointestinal carcinomas (47%), lymphoma/leukemia (7%), carcinomas of prostate (9%), breast (7%), kidney (6%), lung (5%), female genital tract (5%), carcinoid tumors (3%), soft tissue and bone sarcomas (3%), malignant melanoma (2%) and seminoma (1%) (1,3-5).

Since 2002 (FDA approved), imatinib mesylate, a tyrosine kinase inhibitor that competitively inhibits KIT, BCR-ABL, ARG, PDGFR, and PDGFR tyrosine kinases (6-9), has changed the natural history of the disease (10,11) and has become the standard treatment for unresectable metastatic GISTs. Improving longevity in patients with GIST, imatinib introduced questions concerning the development of second primary malignancies (SPMs) in these patients. Different studies have demonstrated a small risk of second cancers in patients receiving therapy with tyrosine kinase inhibitors for hematologic malignancies, especially for chronic myeloid leukemia (CML) (12), but the actual risk of developing SPMs for GIST-patients treated with imatinib is unknown.

Recently, Phan *et al.* (13) have analyzed in a critical way the topic of the incidence of SPMs after GIST in pre-imatinib (1992-2001) and after imatinib (2002-2009) era. They found that the rate of SPMs after GIST in the imatinib era was 7.07%, compared with the rate of 1.15% that occurred in the pre-imatinib era and it was statistically significant ($P=0.030$). Previously, other authors (14) were

involved in the issue; in fact, in a prospective, observational study of imatinib therapy for unresectable and metastatic GISTs (a total of 70 patients were enrolled between December 2001 and December 2009) they found that 10.0% of GIST-patients suffered from second malignancies and they concluded saying that physicians should pay attention to the occurrence of second malignancies during imatinib therapy for GISTs. However, Phan *et al.* (13) are the first to statistically compare pre and post imatinib era. In particular, this difference was mainly accounted for a higher incidence of colon adenocarcinoma in the imatinib era ($P=0.023$). Renal cell carcinoma also accounted for this difference, but the relationship between imatinib and renal cancers is less clear. In contrast, the rate of the melanoma of the skin was significantly lower in the imatinib era compared with pre-imatinib era ($P=0.030$), probably because a small percentage of melanomas demonstrate activating mutations of KIT, for which imatinib demonstrates significant efficacy (15,16).

According to the present knowledge, the main cause for the increased incidence of SPMs in the imatinib era is explained by the increased survival of patients with metastatic GISTs and therefore more time available to develop SPMs, as supposed by other authors (13). This was also confirmed by Phan *et al.* (13): in facts, in the multivariable logistic regression analysis, they found that age was the most important factor related to someone's odds of developing an SPM or not in any time period: patients who were older had a 3.7% greater odds per year of developing an SPM and patients with SPMs were more likely to be alive (62.5%) and with a greater number of months of survival (mean =70.83 months) than those without SPMs (45.68%, mean =39.33 months), and it was statistical significant ($P<0.0001$). In addition the

higher incidence may also be related to increased medical surveillance following primary diagnosis.

However, there is an important limitation concerning diagnosis; in particular GISTs were not able to be distinguished from other gastrointestinal smooth muscle tumors prior to widespread use of c-kit staining, and were often misclassified. Add to this the surveillance bias, which may have affected the incidence of SPMs in patients who already carried a primary diagnosis of cancer. Also we must not forget that we are talking about rare cancers and, therefore, with a lower degree of scientific evidence with respect to the most frequent pathologies.

In conclusion, we can consider the topic of the incidence of SPMs after GIST in pre-imatinib and after imatinib era as clinically relevant. Based on the knowledge available today, the main cause for the increased incidence of SPMs in the imatinib era is explained by the increased survival of patients with metastatic GISTs and therefore more time available to develop SPMs. Nevertheless, it is necessary to investigate the mechanisms leading to the more frequently development of certain tumors than other.

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