Second primary malignances (SPMs) in patients (p) with gastrointestinal stromal tumors (GIST). A coincidence or an effect of Imatinib?

A.Estival[1],O.Etxaniz[1], JL.Cuadra[1], M.Romeo[1], I.Blanco[1], M.Gil[1], S.Ahlal[1], I.Ojanguren[2], A.Indacochea[1], L.Vila[1], C.Balana[1].

[1] Department of Medical Oncology. [2] Department of Pathology. Catalan Institute of Oncology, Hospital Germans Trias i Pujol, Badalona, Spain.

Abstract

Aim: GISTs are the most common mesenchymal tumors of the gastrointestinal tract. Imatinib has become the standard treatment for unresectable metastatic GISTs and as adjuvant treatment in high-risk patients (p). A high rate of second primary malignancies (SPMs) (4.5-33.3%) has been reported in p with sporadic GISTs and a potential association between imatinib treatment and the development of SPMs has been postulated.

Methods: We have retrospectively reviewed the incidence SPMs in all p diagnosed with GIST and treated at a single institution between 1997 and 2012.

Results: A total of 95p were diagnosed with GIST, 21 (22%) of whom developed SPMs. In addition, 18 of the 95 p (18.9%) had premalignant lesions, the most common of which were tubular adenoma (5p) and melanocytic nevus (4p). For the 21 p with SPMs, median age at GIST diagnosis was 62.2 years (range, 27-75). The GIST was located in the stomach in 10p (47.6%) and in the small bowel in 11 (52.4%). The SPMs were in colon (6p), breast (4p), kidney (4p), bladder (3p), head and neck cancer (3p), esophagus (2), lymphoproliferative disease (2), adrenal gland (2p), non-melanoma skin cancer (2p), prostate (1), pancreas (1), bone and soft tissue sarcoma (1p), ovary (1), pheochromocytoma (1p) and oligodendroglioma (1).
7p had more than one SPM. Only 1p had been diagnosed with Neurofibromatosis as a genetic sydrome.
The SPM were metachronous in 17p (81%). Only 4p (19.4%) received imatinib, 2 of whom developed SPMs after treatment.

Conclusions: We have observed SPMs in 19% and premalignant lesions in 18% of p with GISTs.
While the cause of this high rate of SPMs is difficult to determine, it seems that factors other than imatinib may play a role.
Further investigation is warranted.

Corresponding author: Anna Estival.
E-mail: aestival@iconcologia.net

Background

GISTs are rare mesenchymal tumors that usually express c-kit kinase (approximately 90% of cases).
They are the most common mesenchymal neoplasm in gastrointestinal tract.
GIST can be sporadic (up to 95%) or diagnosed within a hereditary syndrome such as type 1 neurofibromatosis, classic familiar GIST syndrome and Carney's syndrome.
In patients with sporadic GIST, a high incidence of SPMs (4.5-33.3%) has been found and several cases have been published.[1,2,3.]
These SPMs are located in gastrointestinal tract (47%), prostate (9%), breast (7%), hematological tumors (7%), kidney (6 %) and lung (5%).
Imatinib mesylate is a tyrosine kinase inhibitor which targets KIT, PDGFR, BCR -ABL and ARG. Imatinib has become the standard treatment for unresectable and metastatic GIST and for high-risk patients in the adjuvant setting.
Since the approval of imatinib, the high incidence of SPMs in patients with GIST has led to speculation about a potential carcinogenic effect of imatinib.[3,4]

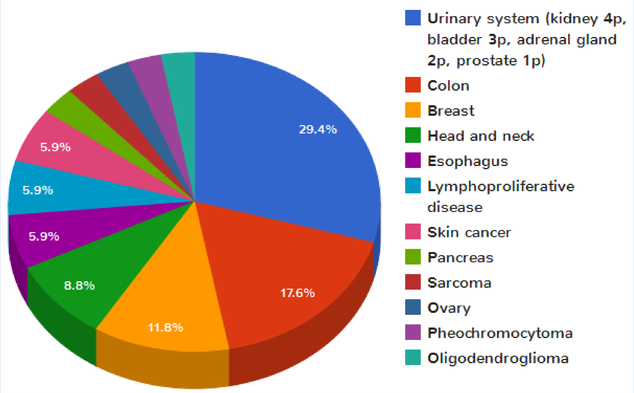
Methods

We have retrospectively analyzed the incidence of synchronous and metachronous SPMs and premalignant lesions, in all patients diagnosed with GIST and treated at a single institution between 1997 and 2012.

Results

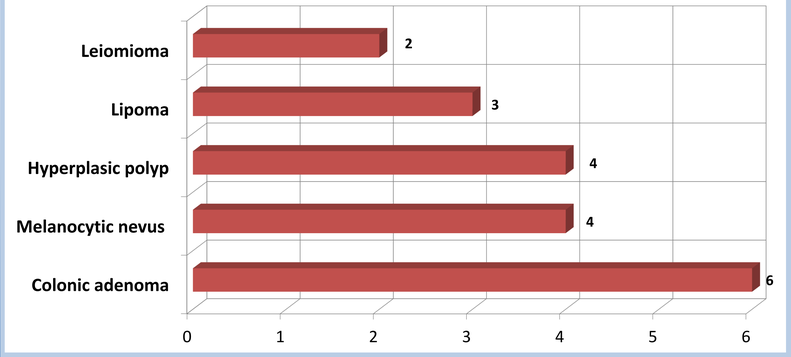
A total of 95 patients were diagnosed with GIST, 34 SPMs were developed in 21 p (22%) and 30 premalignant lesions in 17p. Counting together premalignant and malignant lesions, 29p (30.5%) had some neoplastic disease.
The SPMs were in colon (6p), breast (4p), kidney (4p), bladder (3p), head and neck cancer (3p), esophagus (2), lymphoproliferative disease (2), adrenal gland (2p), non-melanoma skin cancer (2p), prostate (1), pancreas (1), bone and soft tissue sarcoma (1p), ovary (1), pheochromocytoma (1p) and oligodendroglioma (1).
Seven patients had more than one SPM and only one patient was diagnosed with neurofibromatosis as a genetic syndrome.
The SPMs were metachronous in 17 patients (81%) and synchronous in 4. Of the 17 patients with metachronous SPMs, GIST was the first tumor in 9, with a median time of 60.5 months (range, 4-169) between tumors.
GIST was the second tumor in the remaining 8 patients, with a median time to diagnosis of 36.6 months (range, 5-98).

SPMs origin



Three of these 8 patients received chemotherapy as adjuvant treatment for the SPM. The drugs used for the SPM were: docetaxel, cyclophosphamide, fluorouracil and epirubicin in a patient with breast cancer; fluorouracil in a patient with colon cancer; and lomustine and procarbazine in a patient with oligodendroglioma.
17p were diagnosed with premalignant lesions, the most common of lesions were colonic adenoma (6p), melanocytic nevus (4p) and lipoma (3p).
Only 5 of our 29 patients who developed any neoplastic disease (17.2 %) had been treated with imatinib, 3p of whom were diagnosed with malignant lesion after having been treated with imatinib.
The first of these two patients was diagnosed with papillary renal cell carcinoma as a SPM after having been treated for a metastatic GIST with imatinib 400mg/day for 2 years and 10 months and imatinib 800mg/day for 1 year (total 3 years and 10 months of imatinib treatment).
The second patient was diagnosed with prostate adenocarcinoma as a SPM after having been treated with imatinib 400mg/day for 4 months as adjuvant treatment for a high-risk GIST after a R1 resection.
The last patient received imatinib at dose of 400mg/day for 5 months in the metastatic setting before the development of adenomatous hyperplasia in colon. This p also had tubular adenoma previous to GIST.
Until now, five patients had died, four due to progression of the SPM.

Main Premalignant Lesions



Conclusions

To our knowledge this is the first study with Spanish population in p with GIST and SPM.
The incidence of SPM in our population is 22%. Adding the 18.9% of premalignant lesions we have found a 30% of neoplastic disease coexisting with GIST.
An important point is the high incidence of urinary tract neoplasm with 10 p affected (11% of p diagnosed with GIST).
Looking for a possible external carcinogen, we found 3 patients who received chemotherapy as adjuvant treatment before being diagnosed with GIST. Only 3 patients were diagnosed with a neoplastic disease after being treated with imatinib.
The relation-ship between SPMs and GIST is unknown and any study has achieved a consistent conclusion, but it seems unrelated to imatinib.
Nowadays only three hereditary syndromes are known to involve GIST. In our series, only 1 patient had a known hereditary syndrome.
GISTs are tumors with good prognosis, so most patients with SPM and GIST will die as a direct consequence of the SPM.
Further research is needed in order to find new genetic alterations that could help to determine correct follow up for these p and eventually to propose prophylactic strategies.

References

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