Niigata University Hospital is a regional center institution of cancer therapy where many patients with gastrointestinal stromal tumors (GISTs) are visiting to seek the latest treatment. During the time I was treating GIST patients there with imatinib, a tyrosine kinase inhibitor, a small concern was raised: I successively encountered patients who were newly diagnosed as having malignant neoplasms during the course of their treatment. Of the 70 GIST patients who were enrolled in our prospective study of imatinib therapy, seven suffered from second primary malignancies (SPMs). One female GIST patient who suffered from advanced esophageal cancer died of the SPM, whereas the remaining six patients continued with their imatinib therapy and their prognoses were not affected by their SPMs. I reported on the risk of SPMs in GIST patients under imatinib therapy to an international journal of clinical oncology (1). As the patient cohort of our study was so small in number to apply to statistical analysis, our observation was no more than a clinical alert.

In a study published on *Translational Cancer Research*, Phan and colleagues reported on new evidence of the association of SPMs in GIST patients (2). They analyzed the incidence of SPMs in GIST patients on the basis of Surveillance Epidemiology and End Results (SEER), large-scale cancer statistical database organized by the National Cancer Institute of the United States. Their study results can be summarized into three points as follows: (I) GIST patients in the imatinib era [2002-2009] tended to show a higher incidence of SPMs than the general population of the same period; (II) The incidence of SPMs was significantly higher in the cohort of imatinib era than in pre-imatinib era [1992-2001]; (III) The high SPM incidence depended on the presence of gastrointestinal (GI) tract cancer and kidney cancer.

Since the establishment of GIST as a disease entity, researchers worldwide (3-9) have reported its frequent association with other malignant neoplasms. Earlier studies were retrospective ones in which data were collected from the cancer registry or pathological files of each institution. Moreover, the samples in those studies, except for Agaimy’s (4), were small in size, comprising 22-783 patients with GIST. Therefore, the obtained results were not applicable to statistical validation. Previous studies showed that 9-27% of GIST patients developed second malignant neoplasms synchronously or metachronously. The reported incidences of SPMs in these patients appeared to be higher than those in the general population. However, it remains undetermined whether this difference is statistically significant or not. The existence of subclinical GISTs further complicated the issue of SPMs in GIST patients.

Recent studies by refined histopathological analysis have revealed that asymptomatic small GISTs, which are less than ten mm in diameter, are unexpectedly common in the general population. Such subclinical GISTs were found in 22.5% of autopsy cases (10) and 35% of gastric cancer patients who underwent stomach resection (11). Therefore, GISTs are occasionally found at diagnosis or surgery of the other cancers. Many previous studies included cases of such incidentally found GISTs in subjects for analysis. The cases of additionally resected GISTs may be the cause of the overestimation of the association between GIST and other malignant neoplasms.

In the study of Phan et al., the SPM incidence in GIST patients was analyzed on the basis of the SEER data. Their methodology largely excluded publication bias, which enabled them to obtain population-based, epidemiological
results. In this respect, the study of Phan et al. showed significant improvement compared with the series of earlier studies. In addition, as the use of SEER enabled comparison with the general population, the authors estimated whether the higher incidence of SPMs found in GIST patients than in the general population is statistically significant or not. The SPM incidence in GIST patients was 7.07% and the standardized incidence ratio (SIR) to the general population was found to be 1.27 in the study of Phan et al. Despite the statistically marginal significance [95% confidence intervals (CI): 0.96-1.66], the present study has not demonstrate that GIST patients have a substantial risk of developing SPMs. Nevertheless, this underestimation remains a possibility because the nationwide registry tends to overlook second malignancies that occurred late. A global study to validate a new risk classification of GISTs (12) has recently been reported. In that study, data from 10 population-based cohorts were collected worldwide. The use of such large-scale, high-quality data would clarify the SPM incidence in GIST patients.

Phan et al. also addressed another clinically important issue, i.e., the effect of imatinib on SPM occurrence. Imatinib revolutionized GIST treatment; the median survival of advanced GIST patients was increased to nearly five years (13). Because this oral tyrosine kinase inhibitor needs to be taken daily for a long time, the risk of oncogenesis is more critical than that posed by conventional chemotherapeutic agents. Phan et al. divided GIST patients into two cohorts, those in the pre-imatinib era [1992-2001] and those in the imatinib era [2002-2009], and they compared the incidence of SPMs between these two groups of patients. The SPM incidence was significantly higher in the imatinib-era patients than in pre-imatinib-era patients. Although this finding may lead to the suspicion of the oncogenic effect of imatinib in GIST patients, it is shortsighted and dangerous to conclude that imatinib increased the risk of SPMs. In the pre-imatinib era, as the pathological entity of GIST has not yet been established, many cases of GISTs were misdiagnosed as sarcoma of the GI tract. Therefore, Phan et al. collected valid data sets using diagnostic codes that included “leiomyosarcoma” and “neurilemmoma,” which imply that the study cohort may include a considerable number of patients with GI sarcomas other than GIST. Thus, the cohort in the pre-imatinib era is heterogeneous. The comparison of the incidences between the pre-imatinib era and the imatinib era should be considered rather scientifically unsound.

Nevertheless, the study of Phan et al. is noteworthy concerning the association of imatinib with SPMs of GIST patients. They reported that kidney cancer was the third frequent SPM following GI tract cancer and lung cancer. The SIR of kidney cancer was 4.57 (95% CI: 1.68-9.96), which reached a statistically significant level. Kidney cancer is not so common, ranking the eighth highest malignancy according to site (14). In vitro experiments revealed that rats exposed to imatinib for two years showed a significantly increased risk of carcinogenesis in the genitourinary system (15). This finding raised the concern that the risk of kidney cancer would increase in imatinib therapy in clinical settings. Surveillance bias should also be taken into consideration: GIST patients undergoing imatinib therapy are examined by computed tomography. Frequent examination by abdominal imaging may facilitate the detection of latent kidney cancer. Furthermore, kidney cancer was found in GIST patients without imatinib therapy as well (7,16). This suggests that GIST and kidney cancer may share a common genetic background or environmental etiological factors. Large-scale clinical trials were conducted for approval of imatinib for advanced GIST (17); since then, 12 years has passed. A long-term follow-up of the patients enrolled in these trials would be necessary to clarify the relationship between imatinib and SPMs in GIST patients.

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