Malignancies occurring during therapy with tyrosine kinase inhibitors (TKIs) for chronic myeloid leukemia (CML) and other hematologic malignancies

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Success of tyrosine kinase inhibitors (TKIs) in chronic myeloid leukemia (CML) has given patients hope for a long disease-free-survival. A longer survival raises the question of late effects, including development of another malignancy. Records of 1445 patients with CML/myeloproliferative neoplasm or other hematologic malignancies treated with TKIs were reviewed to investigate frequency and characteristics of second malignancies (other than acute myeloid leukemia, acute lymphocytic leukemia, or myelodysplastic syndrome). The number of second cancers was compared with the number expected from the Surveillance, Epidemiology, and End Results database. After a median follow-up of 107 months (range, 13-362 months) after CML/myeloproliferative neoplasm diagnosis, 66 patients (4.6%) developed 80 second cancers, including skin (31%), prostate (15%), melanoma (13%), digestive system (10%), kidney (4%), thyroid (4%), breast (3%), chronic lymphocytic leukemia (3%), hepato-biliary (3%), and other cancers (14%). Excluding nonmelanoma skin cancers, 55 second cancers were seen in 51 (3.5%) of all patients treated. The risk of second cancer was lower than expected (observed-to-expected ratio, 0.6; 95% confidence interval, 0.44-0.81). Second cancers occur in a small percentage of patients receiving therapy with TKIs for hematologic malignancies, mostly CML. No evidence at the moment suggests that exposure to TKIs increases the risk of developing second cancers. (Blood. 2011; 118(16):4353-4358)

Introduction

Imatinib mesylate, a tyrosine kinase inhibitor (TKI), is now standard therapy for patients with chronic myeloid leukemia (CML), and > 80% of patients achieve a complete cytogenetic response (CCyR) and ≥ 70% may achieve a major molecular response (MMR) by 5 years of therapy.1 Newer therapies with other TKIs (eg, dasatinib, nilotinib, bosutinib) are effective after imatinib mesylate failure and more recently have shown superiority as frontline therapy compared with imatinib mesylate.2,8 However, all these medications are usually administered indefinitely (lifetime of patient).9

The various TKIs may have immunomodulatory effects as suggested by the in vitro inhibitory effects on T-cell proliferation and activation by imatinib mesylate, nilotinib, and dasatinib.10-12 On the basis of these effects and its inhibition of the PDGFR pathway and antifibrotic properties, imatinib mesylate is being investigated in the treatment of chronic GVHD with sclerotic features.13 Other TKIs such as dasatinib also inhibit other kinases, such as SRC kinases, that are key regulators of immune responses.14 Dasatinib was in fact originally developed as an immunosuppressive agent.15

The success of TKIs in CML has given patients hope for a long disease-free survival. However, with prolonged survival, questions arise about the possibility of late effects of TKI treatment, including the possibility of developing other malignancies. One previous report suggested an unexpected increased incidence of cancers among patients treated with imatinib mesylate after failure to IFN.16 In response to that report, Novartis (imatinib mesylate manufacturer) reported in a letter that their intracompany epidemiologic analysis showed 110 second primary malignancies in 9518 patients from their global database, with no evidence of increased incidence of prostate cancer or any other malignancy.17 The database for that report continues to mature with a mean time-at-risk for the trial population of 1.16 years (range, 0-4.91 years). These data, although valuable, may be limited because not all instances might be reported, and the follow-up is relatively short. Thus, there is still lack of data about long-term risks of TKI therapy.

We thus analyzed our CML patient population to investigate the frequency and characteristics of second malignancies (other than acute myeloid leukemia, acute lymphocytic leukemia, or myelodysplastic syndrome) among patients with CML or other hematologic malignancies (myeloproliferative neoplasm [MPN]) treated with TKI.

Methods

Patients

All patients with Ph-positive CML or MPN treated with a TKI at M. D. Anderson Cancer Center between November 1998 and April 2010 were included in this analysis. The criteria for various phases of CML were as described.18 All patients were treated with a TKI at various doses as part of a series of phase 1 and phase 2 studies. These studies were approved by The University of Texas M. D. Anderson Cancer Center Institutional Review Board, and all patients signed approved informed consents in accordance with the Declaration of Helsinki.

Submitted June 21, 2011; accepted August 4, 2011. Prepublished online as Blood First Edition paper, August 16, 2011; DOI 10.1182/blood-2011-06-362889. The publication costs of this article were defrayed in part by page charge payment. Therefore, and solely to indicate this fact, this article is hereby marked “advertisement” in accordance with 18 USC section 1734.

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Results

The records of 1445 patients (1342 with CML and 103 with MPN) treated with a TKI were reviewed. The patients with CML included 342 in chronic phase (CP) treated with imatinib mesylate after IFN failure, 338 treated with imatinib mesylate in advanced phases (accelerated phase [AP] or blastic phase), 312 treated with imatinib mesylate as initial therapy (CP or AP), 183 treated with second-generation TKI after imatinib mesylate failure (CP or AP), 167 treated with second-generation TKI as frontline therapy (CP or AP). Of the patients with MPN, 24 had systemic mastocytosis, 24 had polycythemia vera (PV), 22 had hypereosinophilic syndrome, 20 had myelofibrosis, 13 had MPN-unclassifiable, and all of them received imatinib mesylate.

Sixty-six patients (4.6%; 63 CML [4.7%], 3 MPN [2.9%]) developed 80 different second cancers. Of these 66 patients, 41 (62%) were men, including 39 (62%) of the 63 with CML and 2 (67%) of the 3 with MPN. Of the 63 patients with CML who developed malignancies, 34 received frontline therapy for CML with imatinib mesylate, 1 with dasatinib, and 1 with nilotinib, whereas the remaining 27 patients received imatinib mesylate after IFN/other treatment failure. In addition, 7 of the patients with CML received dasatinib, 3 received nilotinib, and 2 received bosutinib after imatinib mesylate failure. None of the 66 patients had received stem cell transplantation, and their characteristics are shown in Table 1. All 3 patients with MPN, who developed second cancers, had PV as their primary diagnosis. The malignancies observed included 15 patients (23%) with 23 nonmelanoma skin cancers (basal cell cancer [BCC] or squamous cell cancer [SCC] or both), and 51 patients (77%) with 57 cases of second cancers (55 cases of other second cancers; ie, cancers other than nonmelanoma skin cancers, and 2 patients had both a nonmelanoma skin cancer and another different second cancer; Table 2). Thirteen of these patients (21%) had a prior diagnosis of cancer, in all instances in remission at the time TKI was initiated; in 2 of them the cancer that occurred after start of TKI was the same as their prior cancer, both of them breast cancer, with initial remission duration of 108 and 112 months by the time of CML diagnosis, and relapsed 39 and 56 months after the start of TKI therapy, respectively.

### Results

The records of 1445 patients (1342 with CML and 103 with MPN) treated with a TKI were reviewed. The patients with CML included 342 in chronic phase (CP) treated with imatinib mesylate after IFN failure, 338 treated with imatinib mesylate in advanced phases (accelerated phase [AP] or blastic phase), 312 treated with imatinib mesylate as initial therapy (CP or AP), 183 treated with second-generation TKI after imatinib mesylate failure (CP or AP), 167 treated with second-generation TKI as frontline therapy (CP or AP). Of the patients with MPN, 24 had systemic mastocytosis, 24 had polycythemia vera (PV), 22 had hypereosinophilic syndrome, 20 had myelofibrosis, 13 had MPN-unclassifiable, and all of them received imatinib mesylate.

Sixty-six patients (4.6%; 63 CML [4.7%], 3 MPN [2.9%]) developed 80 different second cancers. Of these 66 patients, 41 (62%) were men, including 39 (62%) of the 63 with CML and 2 (67%) of the 3 with MPN. Of the 63 patients with CML who developed malignancies, 34 received frontline therapy for CML with imatinib mesylate, 1 with dasatinib, and 1 with nilotinib, whereas the remaining 27 patients received imatinib mesylate after IFN/other treatment failure. In addition, 7 of the patients with CML received dasatinib, 3 received nilotinib, and 2 received bosutinib after imatinib mesylate failure. None of the 66 patients had received stem cell transplantation, and their characteristics are shown in Table 1. All 3 patients with MPN, who developed second cancers, had PV as their primary diagnosis. The malignancies observed included 15 patients (23%) with 23 nonmelanoma skin cancers (basal cell cancer [BCC] or squamous cell cancer [SCC] or both), and 51 patients (77%) with 57 cases of second cancers (55 cases of other second cancers; ie, cancers other than nonmelanoma skin cancers, and 2 patients had both a nonmelanoma skin cancer and another different second cancer; Table 2). Thirteen of these patients (21%) had a prior diagnosis of cancer, in all instances in remission at the time TKI was initiated; in 2 of them the cancer that occurred after start of TKI was the same as their prior cancer, both of them breast cancer, with initial remission duration of 108 and 112 months by the time of CML diagnosis, and relapsed 39 and 56 months after the start of TKI therapy, respectively.

### Evaluation of patients

All patients had a history and physical examination, complete blood counts, and blood chemistry before the start of therapy and every month for the first 3 months, then every 3 months until 12 months from the start of therapy, and then every 6 months. Cytogenetic response was assessed by G-banding assessed in the BM with ≥ 20 metaphases counted, and molecular response was assessed by real-time PCR. Both cytogenetic and molecular response assessments were performed at baseline, every 3 months for the first 12 months, and then at least every 6 months. Response and relapse criteria were as previously reported.  

### Statistical analysis

Overall survival was determined from the start of therapy with TKI to death from any cause or last follow-up. To determine whether the number of patients in our patient cohort who developed malignancies after treatment for CML was excessive, we computed standardized incidence ratios (SIRs). These, essentially, are the ratio of the number of patients who developed subsequent invasive cancers (excluding nonmelanoma skin cancer) in our population (O = observed) compared with the number of cases expected (E = expected) to occur if the US population rates were applied to the same cohort. The latter number was determined with age, sex, and calendar year–specific incidence rates from the SEER (Surveillance, Epidemiology and End Results) data and the relative person-years at risk from our population. To calculate the SIRs (O/E) we used the Cohort Analysis for Epidemiology and End Results program.  

### Table 1. Characteristics of all patients with second cancers during TKI therapy for CML/MPN

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Median (range)</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis of CML/MPN, y</td>
<td>57 (29-78)</td>
<td></td>
</tr>
<tr>
<td>Age at diagnosis of second cancer, y</td>
<td>62 (31-85)</td>
<td></td>
</tr>
<tr>
<td>WBC count at CML/MPN, × 10^9/L</td>
<td>98.9 (12.6-398)</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin level at CML/MPN, g/dL</td>
<td>12.9 (9.18-5)</td>
<td></td>
</tr>
<tr>
<td>Platelet count at CML/MPN, × 10^9/L</td>
<td>427.5 (97-1440)</td>
<td></td>
</tr>
<tr>
<td>Follow-up after CML/MPN, mo*</td>
<td>107 (13-362)</td>
<td></td>
</tr>
<tr>
<td>Time on CML/MPN to second cancer, mo*</td>
<td>46 (3-302)</td>
<td></td>
</tr>
<tr>
<td>Time on treatment with TKI until second cancer, mo*</td>
<td>39 (2-98)</td>
<td></td>
</tr>
<tr>
<td>Time on imatinib until second cancer (n = 64), mo*</td>
<td>39 (0.7-98)</td>
<td></td>
</tr>
<tr>
<td>Time on dasatinib until second cancer (n = 8), mo*</td>
<td>6.5 (0.3-22)</td>
<td></td>
</tr>
<tr>
<td>Time on nilotinib until second cancer (n = 4), mo*</td>
<td>9 (3-14)</td>
<td></td>
</tr>
<tr>
<td>Time on bosutinib until second cancer, (n = 2), mo*</td>
<td>7 (3-20)</td>
<td></td>
</tr>
<tr>
<td>Follow-up after diagnosis of second cancer, mo*</td>
<td>30 (1-121)</td>
<td></td>
</tr>
<tr>
<td>History of cancer before TKI therapy</td>
<td>13 (20)</td>
<td></td>
</tr>
<tr>
<td>Duration of CR for previous cancers, mo</td>
<td>114.5 (9-471)</td>
<td></td>
</tr>
</tbody>
</table>
| WBC indicates white blood cell; and CR, complete remission.  
*Data reflect time to/from first second cancer identified.  

### Table 2. Patients with CML/MPN who developed various second cancers during TKI therapy

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>CML</th>
<th>MPN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no.</td>
<td>66</td>
<td>3</td>
</tr>
<tr>
<td>Nonmelanoma skin cancer (BCC or SCC or both), n (%)</td>
<td>15 (23)</td>
<td>1 (33)</td>
</tr>
<tr>
<td>Other second cancers, n (%)</td>
<td>51 (77)</td>
<td>2 (67)</td>
</tr>
<tr>
<td>CML after IFN</td>
<td>27</td>
<td>6</td>
</tr>
<tr>
<td>TKI as frontline</td>
<td>36</td>
<td>1</td>
</tr>
<tr>
<td>MPN after Phleb.</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Therapy for CML</td>
<td>49 (78)</td>
<td>22 (81)</td>
</tr>
<tr>
<td>Therapy for MPN</td>
<td>27 (75)</td>
<td>NA</td>
</tr>
<tr>
<td>P after Phleb.</td>
<td>2 (100)</td>
<td>NA</td>
</tr>
</tbody>
</table>

P indicates radioactive phosphorus; Phleb, phlebotomies; and NA, not applicable.  
*Nine patients with 1 skin cancer, 4 with 2, and 2 with 3 skin cancers (total 23 cancers).  
†Forty-five patients with 1 other second cancer, 4 with 2 other second cancers, 2 with other second cancer + nonmelanoma skin cancer (55 nonskin cancers, and 2 nonmelanoma skin cancers).  
‡Eight patients with 1 skin cancer, 4 with 2 cancers, and 2 with 3 cancers (total 22 cancers).  
§Forty-three patients with 1 other second cancer, 4 with 2 other second cancers, 2 with other second cancer + nonmelanoma skin cancer (53 nonskin cancers, and 2 with nonmelanoma skin cancers).
Table 3. Types of second cancers during TKI therapy and their treatment

<table>
<thead>
<tr>
<th>Type of second cancer during TKI therapy</th>
<th>No. of patients (n = 80)*</th>
<th>CML/MPN status at time of second cancer</th>
<th>Therapy given for second cancer</th>
<th>Response of second cancer to therapy</th>
<th>Relapse/advanced second cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma</td>
<td>10</td>
<td>CMR: 2, MMR: 2, CCyR: 4, CHR: 2</td>
<td>Surg: 9; surg + XRT + drugs: 1</td>
<td>CR: 10</td>
<td>None</td>
</tr>
<tr>
<td>GI cancer (colon + gastric + esophageal)</td>
<td>8 (4 + 2 + 2)</td>
<td>CMR: 2, MMR: 3, CCyR: 1, CHR: 2</td>
<td>Surg: 1, drugs: 1, observe: 3, surg + drugs: XRT: 3</td>
<td>CR: 5, no change: 3</td>
<td>None</td>
</tr>
<tr>
<td>GU cancer (urinary bladder + kidney)</td>
<td>4 (1 + 3)</td>
<td>CMR: 2, CCyR: 2</td>
<td>Surg: 2, observe: 1, drugs: 1</td>
<td>CR: 2, no change: 1, unknown: 1</td>
<td>Unknown: 1</td>
</tr>
<tr>
<td>Thyroid cancer</td>
<td>3</td>
<td>CMR: 1, MMR: 1, CCyR: 1</td>
<td>Surg</td>
<td>CR</td>
<td>None</td>
</tr>
<tr>
<td>Breast cancer (relapse + new†)</td>
<td>4 (2 + 2)</td>
<td>MMR: 2, PCyR: 1, PV: 1</td>
<td>Drugs: 1, drugs + XRT: 1 drugs + XRT + surg: 2</td>
<td>CR: 1, unknown: 1, mets: 2</td>
<td>Mets in the relapse patients: 2</td>
</tr>
<tr>
<td>CLL</td>
<td>2</td>
<td>MMR: 1, CCyR: 1</td>
<td>Observe</td>
<td>No change</td>
<td>None</td>
</tr>
<tr>
<td>GI cancer (hepatobiliary)†</td>
<td>2</td>
<td>CHR: 1, MMR: 1</td>
<td>Drugs: 1, drugs + XRT: 1</td>
<td>No change: 2</td>
<td>Mets: 1</td>
</tr>
<tr>
<td>GU cancer (ovarian + uterine)</td>
<td>2 (1 + 1)</td>
<td>MMR: 1, CP: 1</td>
<td>Surg: 1, Surg + XRT: 1</td>
<td>CR: 2</td>
<td>None</td>
</tr>
<tr>
<td>Head and neck cancer</td>
<td>2</td>
<td>MMR: 1, CCyR: 1</td>
<td>Surg: 1, observe: 1</td>
<td>CR: 1, no change: 1</td>
<td>None</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>1</td>
<td>CHR</td>
<td>Surg</td>
<td>CR</td>
<td>None</td>
</tr>
<tr>
<td>Lymphoma (large B cell)</td>
<td>1</td>
<td>CMR</td>
<td>Drugs + XRT</td>
<td>CR</td>
<td>None</td>
</tr>
<tr>
<td>MPN</td>
<td>1</td>
<td>CMR</td>
<td>Anagrelide</td>
<td>No change</td>
<td>None</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>1</td>
<td>CCyR</td>
<td>Observation</td>
<td>No change</td>
<td>Mets</td>
</tr>
<tr>
<td>Thymoma</td>
<td>1</td>
<td>MMR</td>
<td>Surg</td>
<td>CR</td>
<td>None</td>
</tr>
<tr>
<td>Cancer of unknown primary</td>
<td>1</td>
<td>MyBP</td>
<td>None</td>
<td>Mets to BM</td>
<td>None</td>
</tr>
<tr>
<td>Skin cancer (BCC/SCC)</td>
<td>25</td>
<td>CMR: 4, MMR: 4, CCyR: 2, PCyR: 3, CHR: 8, CP: 2, AP: 2</td>
<td>Surg: 24, observe: 1</td>
<td>CR: 24, no change: 1</td>
<td>None</td>
</tr>
</tbody>
</table>

CMR, complete molecular response; CHR, complete hematologic response; Surg, surgery; XRT, radiation therapy; drugs, drug therapy; CR, complete remission; mets, metastasis; GI, gastrointestinal; GU, genitourinary; PCyR, partial cytogenetic response; CLL, chronic lymphocytic leukemia; and MyBP, myeloid blast phase.

*Patients counted = 2 times if they developed ≥ 2 second cancers

†Two patients with MPN: 1 developed a new breast cancer and 1 had cholangiocarcinoma.
The most common second cancers were nonmelanoma skin cancers (BCC and SCC), representing 31% of all cancers; these were generally treated with simple or wide excision and cured. The details of various types of second cancers that developed are shown in Table 3. Of the 49 patients with CML with other second cancers (ie, cancers other than nonmelanoma skin cancers), 43 patients (88%) had 1 additional second cancer, 4 patients (8%) had 2 additional other second cancers, and 2 patients (4%) had 1 additional other second cancer plus a skin cancer (SCC) besides the CML. There were 4 patients with CML with 2 second cancers other than nonmelanoma skin cancers diagnosed at different time points. These included 1 patient with melanoma and CLL, 2 patients with melanoma and prostate cancer, and 1 patient with prostate cancer and CLL. Importantly, all the melanoma cases occurred in white patients. The treatments given for these cancers and the responses to treatment are depicted in Table 3. The skin cancers and melanomas were scattered and not localized to any particular anatomical site. Two patients with CML were diagnosed with flow cytometry after showing abnormal peripheral blood cell counts while still maintaining CCyR on imatinib mesylate and had received imatinib mesylate for 65 and 70 months before diagnosis of CLL.

The median time from start of TKI therapy to diagnosis of the initial second cancer was 39 months (range, 2-98 months). The best response to TKI at the time of detection of the second cancer, was CHR in 16 patients (20%), minor cytogenetic response in 3 patients (4%), partial cytogenetic response in 4 patients (5%), and CCyR in 52 patients (65%). The outcome of CML/MPN after the development of other second cancers (cancers other than nonmelanoma skin cancers) was mostly unchanged or with continued improvement of response, with loss of response in only 1 of 55 patients (2%) and unknown outcome in 1 patient with MPN (Table 4). The 1 patient with CML who lost response had received imatinib mesylate for 62 months and dasatinib for 10 months, had only a CHR at the time of developing adenocarcinoma of the rectum, did not receive any therapy for the second cancer, continued dasatinib, lost his CHR, and finally died in AP after 10 months. For the 25 patients (24 with CML and 1 with MPN) with nonmelanoma skin cancers (BCC and/or SCC), 23 (92%) maintained their CML/MPN response, and 2 (8%) with CML had improvement in their response.

After a median follow-up of 30 months (range, 1-121 months) from diagnosis of a second cancer, 12 patients (18%) have died (all CML). Among them, 10 died of CML-related causes, 1 of pancreatic cancer, and 1 of cholangiocarcinoma. Of the 54 patients (51 with CML, 3 with MPN) who are alive, 50 patients with CML (98%) continue on therapy with TKI after the diagnosis of the second cancer, with 24 (47%) in CMR, 20 (39%) in MMR without CMR, 2 (4%) with CCyR without MMR, and 4 (8%) having only CHR. Of the patients receiving TKI as initial therapy for CML who are alive with a second cancer (n = 32), 19 (59%) are in CMR, 9 (28%) in MMR, 2 (6%) in CCyR without MMR, and 2 (6%) with CHR only.

We also calculated the SIRs from the observed number of cases with second cancers compared with the expected number from the SEER data (Table 5). Among the 63 patients with CML, there were 49 patients with other second cancers (second invasive malignancies) and 44 patients with second cancers diagnosed > 12 months after treatment were included in the analysis. The number of other second cancers observed was smaller than expected in this patient population (SIR, 0.6; 95% CI, 0.44-0.81). Analyzing the SIR by age, sex, and treatment with TKI, we observed that the SIR was < 1 in the majority of cases, with the exception of cancer of unknown primary where the SIR was 0.7 (95% CI, 0.36-1.32). The SIR for cancer of unknown primary was statistically significant (p < 0.05).

### Table 4. Outcome of CML/MPN after development of second cancer

<table>
<thead>
<tr>
<th>Second cancer type (n = 80)*</th>
<th>No.</th>
<th>Dose reduce or stop Rx, n</th>
<th>Maintained, n</th>
<th>Improved, n</th>
<th>Lost, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate cancer</td>
<td>12</td>
<td>None</td>
<td>10</td>
<td>2</td>
<td>None</td>
</tr>
<tr>
<td>Melanoma</td>
<td>10</td>
<td>None</td>
<td>8</td>
<td>2</td>
<td>None</td>
</tr>
<tr>
<td>GI cancer (colon + gastric + esophageal)</td>
<td>8</td>
<td>2</td>
<td>7</td>
<td>2</td>
<td>None</td>
</tr>
<tr>
<td>GU cancer (urinary bladder + kidney)</td>
<td>4</td>
<td>None</td>
<td>4</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Thyroid cancer</td>
<td>3</td>
<td>None</td>
<td>2</td>
<td>1</td>
<td>None</td>
</tr>
<tr>
<td>Breast cancer (relapse + new)</td>
<td>4</td>
<td>None</td>
<td>None</td>
<td>3</td>
<td>1 unknown</td>
</tr>
<tr>
<td>CLL</td>
<td>2</td>
<td>None</td>
<td>2</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>GI cancer (hepatobiliary)</td>
<td>2</td>
<td>None</td>
<td>2</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>GU cancer (ovarian + uterine)</td>
<td>2</td>
<td>None</td>
<td>None</td>
<td>2</td>
<td>None</td>
</tr>
<tr>
<td>Head and neck cancer</td>
<td>2</td>
<td>None</td>
<td>1</td>
<td>1</td>
<td>None</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Lymphoma (large B cell)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>MPN</td>
<td>1</td>
<td>None</td>
<td>1</td>
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<tr>
<td>Pancreatic cancer</td>
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<td>None</td>
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<tr>
<td>Thymoma</td>
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<td>None</td>
<td>1</td>
<td>None</td>
</tr>
<tr>
<td>Cancer of unknown primary</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Skin cancer (BCC/SCC)</td>
<td>25</td>
<td>None</td>
<td>23</td>
<td>2</td>
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</tr>
</tbody>
</table>

Rx indicates treatment; GI, gastrointestinal; and GU, genitourinary.
*Patients counted ≥ 2 times if they developed ≥ 2 second cancers.

### Table 5. Comparison of the patients with CML with second cancers other than nonmelanoma skin cancers with the SEER data

<table>
<thead>
<tr>
<th>Variable*</th>
<th>O</th>
<th>E</th>
<th>SIR (O/E)</th>
<th>95% CI for O/E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>44</td>
<td>73</td>
<td>0.60</td>
<td>0.44-0.81</td>
</tr>
<tr>
<td>Men</td>
<td>30</td>
<td>45</td>
<td>0.67</td>
<td>0.45-0.95</td>
</tr>
<tr>
<td>Women</td>
<td>14</td>
<td>28</td>
<td>0.50</td>
<td>0.27-0.84</td>
</tr>
<tr>
<td>Age ≥ 60 y</td>
<td>23</td>
<td>34</td>
<td>0.68</td>
<td>0.43-1.01</td>
</tr>
<tr>
<td>Age &lt; 60 y</td>
<td>21</td>
<td>40</td>
<td>0.53</td>
<td>0.32-0.80</td>
</tr>
</tbody>
</table>

*Analysis conducted for the first invasive second cancers (second cancers other than nonmelanoma skin cancers).
Discussion

With the success of TKI therapy, more patients with CML are now achieving molecular and cytogenetic responses than what was achieved previously in the IFN era, and this has translated into an improved survival. As a result of this, patients with CML are no longer dying from, but with CML, and are living long enough to get other medical problems. The long-term effects of prolonged TKI therapy are still being assessed because imatinib mesylate became standard frontline therapy only in 2001, and therapy is continued indefinitely.

A 2-year preclinical study in rats on oral carcinogenicity of imatinib mesylate at doses of 15, 30, and 60 mg/kg showed neoplasic changes in kidneys, urinary bladder, urethra, preputial and clitoral glands, small intestine, parathyroid glands, adrenal glands, and nonglandular stomach. Renal adenoma/carcinoma, urinary bladder and urethra papillomas, small intestine adenocarcinoma, parathyroid glands adenoma, benign and malignant medullary tumors of the adrenal glands, and papilloma/carcinoma of nonglandular stomach were observed at 60 mg/kg per day, representing ~1.7 times and 1 time the human daily exposure (according to area under curve) at 400 and 800 mg per day, respectively. Papilloma/carcinoma of the preputial/clitoral glands was noted at doses 30 mg/kg per day and higher, representing ~50% of the human daily exposure (according to area under curve) at 400 mg per day. Because these findings were based on rat models, their relevance for humans is not known.

The incidence of second cancers has been investigated after other interventions for CML and other leukemias. In a multiple institutional cohort of 28,874 allogeneic transplant recipients (26% had CML, and 74% had other leukemias) the investigators reported 189 second cancers. Their analysis suggested that patients developed new solid cancers at twice the rate expected on the basis of general population rates (observed-to-expected ratio, 2.1; 95% CI, 1.8-2.5). Significantly increased risks were observed for tumors of oral cavity, liver, brain and CNS, thyroid, bone, soft tissue, and melanoma of the skin. In an analysis of 112 pediatric patients after hematopoietic stem cell transplantation (5% had CML, and 95% had leukemias), 8 patients (7%) developed second cancers: 3 brain/CNS cancers, 1 tongue cancer, 2 melanomas, 1 abdominal tumor, 1 uterine cancer, and 1 testicular cancer (1 patient had 2 cancers).

In another study of 4318 allogeneic transplantations for patients with acute myeloid leukemia and CML, 66 solid cancers were observed at a median of 6 years after transplantations. This study suggested that transplant recipients had 1.4 times higher rates of invasive solid cancers than did the general population (95% CI, 1.08-1.79; \( P = .01 \)). Significantly elevated risks were observed for tumors of the oral cavity, esophagus, lung, soft tissue, and brain. In a meta-analysis of cancer incidence after HIV/AIDS versus immunosuppressed solid-organ transplant recipients (kidney, liver, heart), the investigators found increased rates of all AIDS-defining cancers, as well as those of lymphoma, cancers of liver, stomach, lung, kidney, bladder, myeloma, leukemia, melanoma in both these patient populations; whereas rates of other epithelial cancers (breast, prostate, colon) were the same or lower as the general population. The investigators concluded that increased rates of cancers were found at a very large range of sites and that immune deficiency, regardless of the mechanism of this deficiency, were responsible for the increased risk. There have also been scattered reports of coexistence of CML with other lymphoid malignancies such as CLL and multiple myeloma.

In our analysis, the overall SIR of second cancers was 0.60 (95% CI, 0.44-0.81), suggesting a lower than expected rate of malignancies in patients treated with TKI, although the incidences of melanoma, endocrine tumors, kidney cancers, and CLL were higher than expected. Our results are in contrast to the observations by Roy et al of an unexpected increase in cancers among patients treated with imatinib mesylate. The reason for these discordant results is not known. Considering the long-term therapy with TKI required for patients with CML, it is reassuring that no increased occurrence of malignancies is observed. It is tempting to speculate that the lack of increased incidence of cancers might be applicable to all TKI, but this needs to be confirmed because some agents (eg, dasatinib) may have more immunosuppressive properties that might affect the development of second cancers, although no such effect has been reported to date. Thus, continued observation is required to investigate a possible further delayed effect.

In conclusion, second cancers occur in a small percentage of patients receiving therapy with TKI for hematologic malignancies, mostly CML. Analyzed in the context of the underlying lifetime risk of developing cancer by the general population and in patients who survive cancer, no evidence at the moment suggests that exposure to TKIs is carcinogenic. Continued long-term monitoring of these patients and reporting of any patients who develop second cancers are warranted to further define any possible longer-term risks.

Acknowledgments

This work was supported in part by National Institutes of Health grant CA049639 to J.C.

Authorship

D.V. wrote the manuscript, analyzed data, and approved the manuscript; J.C. designed the study, managed the patients, analyzed data, and reviewed approved the manuscript; S.S.S. assisted with data analysis; and H.K., M.B.R., E.J., A.Q.-C., S.V., F.R., and S.O. managed the patients, analyzed data, and reviewed approved the manuscript; J.C. designed the study, managed the patients, analyzed data, and reviewed approved the manuscript.

Conflict-of-interest disclosure: H.K. and J.C. have research grants from Novartis, BMS, and Pfizer. J.C. is a consultant for Novartis, BMS and Pfizer. The remaining authors declare no competing financial interests.

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Malignancies occurring during therapy with tyrosine kinase inhibitors (TKIs) for chronic myeloid leukemia (CML) and other hematologic malignancies

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