

# A Phase II Trial of Imatinib Mesylate in Merkel Cell Carcinoma (Neuroendocrine Carcinoma of the Skin)

## A Southwest Oncology Group Study (S0331)

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**Background:** Imatinib mesylate (Gleevec) was evaluated as a treatment for Merkel cell carcinoma (MCC, neuroendocrine carcinoma of the skin) based on the identification of strong c-KIT staining of these neoplasms.

**Methods:** Eligibility included patients with measurable metastatic or unresectable MCC, c-KIT (CD117) expression and a Zubrod performance status of 0 to 2. Imatinib 400 mg daily was administered orally in 28-day cycles to 23 patients.

**Results:** Overall, imatinib was well tolerated with grade 1 or 2 nausea, diarrhea, and hematologic toxicity as the most frequent side effects. A partial response was seen in 1 patient (4%; 95% CI: 0%–22%). Median progression-free survival was 1 month (95% CI: 1–2 months). Median overall survival was 5 months (95% CI: 2–8 months). One patient achieved a partial response and another had prolonged disease stabilization while receiving treatment.

**Conclusions:** The majority of patients progressed rapidly within 1 to 2 cycles of treatment. The observed progression-free survival and overall survival were not adequate to conclude that this agent was active in advanced MCC, and thus the planned second stage of patient accrual was not opened.

**Key Words:** Merkel cell carcinoma, neuroendocrine carcinoma of the skin, imatinib mesylate, c-KIT

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Merkel cell carcinoma (MCC) was initially described as a rare neuroendocrine tumor of the skin by Toker in 1972.<sup>1</sup> MCC generally presents initially as a small, firm, asymptomatic reddish or purplish skin nodule.<sup>1–4</sup> Telangiectasia or ulceration may be seen. Initially the clinical behavior of these tumors was thought to be favorable despite their ominous small cell appearance on histologic sections.<sup>2</sup> It has subsequently been established that this tumor is one of the most aggressive forms of skin cancer with a 5-year survival of less than 75%.<sup>5–7</sup> MCC often recurs locally after surgery alone and

has a high risk of both regional lymph node involvement and distant metastases.<sup>8</sup>

Although the term “cutaneous neuroendocrine carcinoma” is potentially a more precise description of these tumors,<sup>3,4</sup> these tumors are still frequently referred to as MCC and that nomenclature was retained in this study. Typically, the tumor presents in middle-aged to elderly patients, but younger patients in their teens and early adulthood have been described.<sup>1,3,4</sup> The incidence in men and women appears to be similar. Risk factors for MCC appear to include both sun exposure and immunosuppression, including following organ transplantation and HIV infection.<sup>9</sup> Despite elaborate pathologic studies, it is still not certain that the Merkel cell is actually the cell of origin of this neoplasm.<sup>9</sup> In fact, the early descriptions characterized this tumor as an undifferentiated carcinoma.<sup>1</sup> Anatomically, Merkel cells have a different body distribution than the most common locations of primary tumors and they lack neurofilament proteins.<sup>9</sup> The original Memorial Sloan-Kettering Cancer Center staging system described stages I-III.<sup>7</sup> Stage I represented primary skin tumors (stage 1A  $\leq 2$  cm, stage 1B  $> 2$  cm). Stage II represented regional lymph node involvement, and stage III was applied to systemic disease, including distant lymph node involvement. This staging system was subsequently modified to a TNM staging system for nonmelanoma skin cancer, using the 4-tier format of the American Joint Committee on Cancer AJCC sixth edition 2002, by promoting stage IB to stage II.<sup>10</sup>

In addition, the trabecular appearance of MCC described by Toker, whereas often equated with MCC, actually classifies only a subset of the tumors. More recently, Gould described a classification of MCC based on predominant patterns of trabecular, intermediate or small cells.<sup>3</sup> Most tumors are a mixture of these patterns although a large series from Memorial Sloan-Kettering identified the intermediate cell type as predominating in most of their patients.<sup>11</sup> These subtypes are not yet known to have definite prognostic significance.

MCC frequently expresses c-KIT CD117.<sup>12–15</sup> For example, Su et al evaluated c-KIT expression in 22 biopsies of MCC, demonstrating expression in 95%.<sup>12</sup> Imatinib mesylate (Gleevec, formerly STI-571) is a small molecule that has been demonstrated to be a highly selective inhibitor of certain receptor tyrosine kinases (RTK), including c-KIT (CD117). We therefore designed a phase II trial of imatinib to test its clinical effectiveness in MCC. Because there are few effective treatments for patients with surgically incurable MCC, identification of an additional active drug would represent an important therapeutic advance. In addition, this study represented an attempt to establish whether multi-institutional trials in this rare disease are feasible in the United States.

## MATERIALS AND METHODS

### Patient Eligibility

Patients enrolled in this trial were required to have biopsy proven MCC (Cutaneous Neuroendocrine Carcinoma) that was

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metastatic or unresectable. Tumor expression of c-KIT (by immunohistochemistry) and a history of a previous skin primary were required (to exclude metastatic small cell carcinoma of noncutaneous origin). Patients with an unknown primary site were, therefore, not eligible. Patients were required to have at least 1 site of measurable disease. Patients with treated, stable, asymptomatic brain metastases were allowed on study. All radiotherapy, chemotherapy, biologic therapy or any other investigational drug treatment was required to be completed at least 28 days before registration. Patients were not allowed to have had major surgery within 14 days before registration. Additional eligibility requirements included: adequate hematologic, renal, and hepatic function and a Zubrod performance status  $\leq 2$ . Patients with a second malignancy, as well as women who were pregnant or nursing were excluded from the study. Patients with class 3/4 cardiac problems by the New York Heart Association Criteria were not eligible, nor were patients taking therapeutic doses of coumadin (warfarin) or those with severe and/or uncontrolled concurrent medical disease. All patients provided written acknowledgment of informed consent in accordance with institutional and federal guidelines.

### Treatment Schedule

Imatinib mesylate (Gleevec) was administered at a dose of 400 mg p.o. daily. One cycle was defined as 28 days regardless of treatment delays. The intent was to administer imatinib continually without interruptions between cycles. Drug was supplied by the NCI through a CRADA collaborative agreement between the National Cancer Institute and Novartis Pharmaceuticals Corporation.

### Toxicity Assessment and Dose Modifications

Toxicity was defined by National Cancer Institute Common Terminology Criteria for Adverse Events Version 3.0. Dosage modifications were performed for hematologic and nonhematologic toxicities. Imatinib was held for a absolute neutrophil count  $< 1000$ , platelet count  $< 50,000$  or nonhematologic grade 2 toxicity. Once toxicity resolved to grade  $\leq 1$  treatment resumed at 400 mg per day. Dose reductions were implemented if neutropenia, thrombocytopenia or nonhematologic grade 2 toxicity recurred with subsequent cycles. Following the second occurrence, imatinib was resumed at 300 mg per day after improvement to grade  $\leq 1$ . If neutropenia, thrombocytopenia or nonhematologic grade 2 recurred, dosing was again held then resumed at 200 mg once resolved to grade  $\leq 1$ . For the first occurrence of nonhematologic grade 3 or 4 toxicity, imatinib was held until resolved to grade  $\leq 1$  and then restarted at 300 mg. If grade 3 or 4 toxicity recurred at the reduced dose the imatinib was again held until toxicity resolved to grade  $\leq 1$  then treatment resumed at 200 mg per day. The use of cytokines (G-CSF or GM-CSF) as well as epoietin alfa was allowed at the discretion of the treating investigator. Initial response assessment was planned at 1 and 2 months after initiation of imatinib therapy.

### Statistical Methods

The primary goal of this study was to evaluate the true response probability (confirmed and unconfirmed, complete and partial responses as defined using RECIST criteria).

It was assumed that imatinib would not be of further interest if the true response probability was less than 5%, and would generate definite interest in further study if 20% or more. A 2-stage enrollment was planned with 20 patients to be accrued initially. If more than 1 response was seen and toxicities appeared acceptable, an additional 20 patients would be accrued. Five or more responses of 40 eligible patients would be sufficient evidence to warrant further study, providing other factors, such as toxicity, progression-free survival, and overall survival were also favorable. The design had a significance level of 5% and a power of 92%. Forty patients

**TABLE 1. Patient Characteristics**

	Patients	Percent
Gender		
Male	17	74%
Female	6	26%
Median age (yr) (range)	77	(57–92)
Zubrod performance status		
0	11	48%
1	9	39%
2	3	13%
Prior treatment		
Surgery	21	91%
Radiation therapy	16	70%
Chemotherapy	14	61%
No prior treatment	1	4%
Sites of disease at baseline		
Primary site		
Limb/extremity	12	52%
Head and neck	9	39%
Trunk	2	9%
Metastatic involvement		
Lymph node/skin/soft tissue	17	74%
Lung	5	22%
Liver	5	22%
Bone	1	4%
Other	7	30%

would be sufficient to estimate toxicity rates to within  $\pm 15\%$  (95% confidence interval). Any toxicity occurring with at least 5% probability was likely to be observed once (87% chance). Progression-free and overall survival probabilities were estimated using the method of Kaplan-Meier.<sup>16</sup>

### RESULTS

From December 2003 to October 2006, a total of 25 patients were accrued to this trial from 13 institutions with 6 accrued through Intergroup participation by the Eastern Cooperative Oncology Group. Two patients were found to be ineligible (one whose tumor was found not to express CD117 on central pathology review, and 1 without measurable disease). Therefore 23 patients were included in the analysis. The accrual rate compared favorably to SWOG's previous trial in this population (S9716), which enrolled only 6 patients over 2 years, and suggests that future trials in this patient population are feasible. Patient demographics are included in Table 1. Median age was 77.1 (with a range of 56.9–91.9 years). Seventeen patients (74%) were men, 6 (26%) were women and all were white. It should be noted that this was a heavily pretreated patient population. Over 60% had progressed following prior chemotherapy. Only 4% of patients had received no prior chemotherapy or radiotherapy.

Toxicity in this trial was typical for clinical trials of imatinib (Table 2). There were 3 episodes of grade 4 toxicities (one each of dyspnea, hyperglycemia, and vomiting). Three patients experienced grade 3 toxicities including 1 episode each of peripheral edema, fatigue, lymphopenia, and rash. Grade 1 to 2 toxicities were mostly hematological and gastrointestinal, and included 4 patients with diarrhea, 6 patients with nausea, 12 with anemia (hemoglobin), 4 with leukopenia, and 4 patients with hypokalemia. There were no complete responses (0%) and 1 confirmed partial response (4%) in

**TABLE 2.** Number of Patients With a Given Type and Grade of Adverse Event

Adverse event	Grade					
	0	1	2	3	4	5
Anorexia	20	1	2	0	0	0
Constipation	20	2	1	0	0	0
Creatinine	20	3	0	0	0	0
Diarrhea	19	4	0	0	0	0
Dyspnea	22	0	0	0	1	0
Edema-limb	20	1	1	1	0	0
Fatigue	20	2	0	1	0	0
Hemoglobin	11	7	5	0	0	0
Hyperglycemia	21	0	1	0	1	0
Hypokalemia	19	4	0	0	0	0
Leukocytes	19	3	1	0	0	0
Lymphopenia	20	1	1	1	0	0
Nausea	17	4	2	0	0	0
Platelets	20	3	0	0	0	0
Rash	22	0	0	1	0	0
Vomiting	20	2	0	0	1	0
Maximum grade any adverse event						
Number	3	7	7	3	3	0

the 23 evaluable patients (4% objective response rate, CI: 0%–22%). In addition, stable disease was observed in 3 patients (9, 4, and 3 months). At the time of analysis, all evaluable patients had developed progressive disease. The estimated median progression-free survival was 1 month (95% CI: 1–2 months), with an estimated 6-month PFS of 4% (95% CI: 0%–13%) (Fig. 1A). The estimated median overall survival was 5 months (95% CI: 2–8 months) (Fig. 1B). The estimated 1-year overall survival was 17% (95% CI: 0%–33%). There were 3 deaths on study, all were attributed to progressing tumor.

DNA sequencing of c-KIT was performed on tumor tissue from 3 nonresponding patients and the 1 patient with long-term stable disease (9 months). All were wild-type and none demonstrated an activating mutation in c-KIT. Unfortunately, the patient with partial response withdrew consent for the study and DNA sequencing could not be performed.

## DISCUSSION

The majority of MCCs are located on the head and neck region.<sup>1,2,4,11,17</sup> Other less frequent sites include the extremities (40%) and the trunk (10%). Anatomic distribution of MCC appears to correlate with chronic exposure to ultra violet radiation. MCC has a high propensity to recur locally and to have both regional and distant metastases. Its biology is reminiscent of the behavior of other small cell neuroendocrine cancers.<sup>1,3–5,18</sup> In 1 study, factors found to predict a lower survival rate included large tumor size, histologic small cell type, and high mitotic rate.<sup>19</sup> Disseminated metastases occur in over 30% of the patients, and may involve liver, lung, bone, and brain.

Recently, the clonal integration of a new human polyoma virus, which was termed Merkel cell polyomavirus (MCPyV), has been reported in 8 of 10 MCC patients.<sup>20</sup> Kassem subsequently studied the formalin-fixed and paraffin-embedded tissue specimens of 39 MCC for the presence of MCPyV by polymerase chain

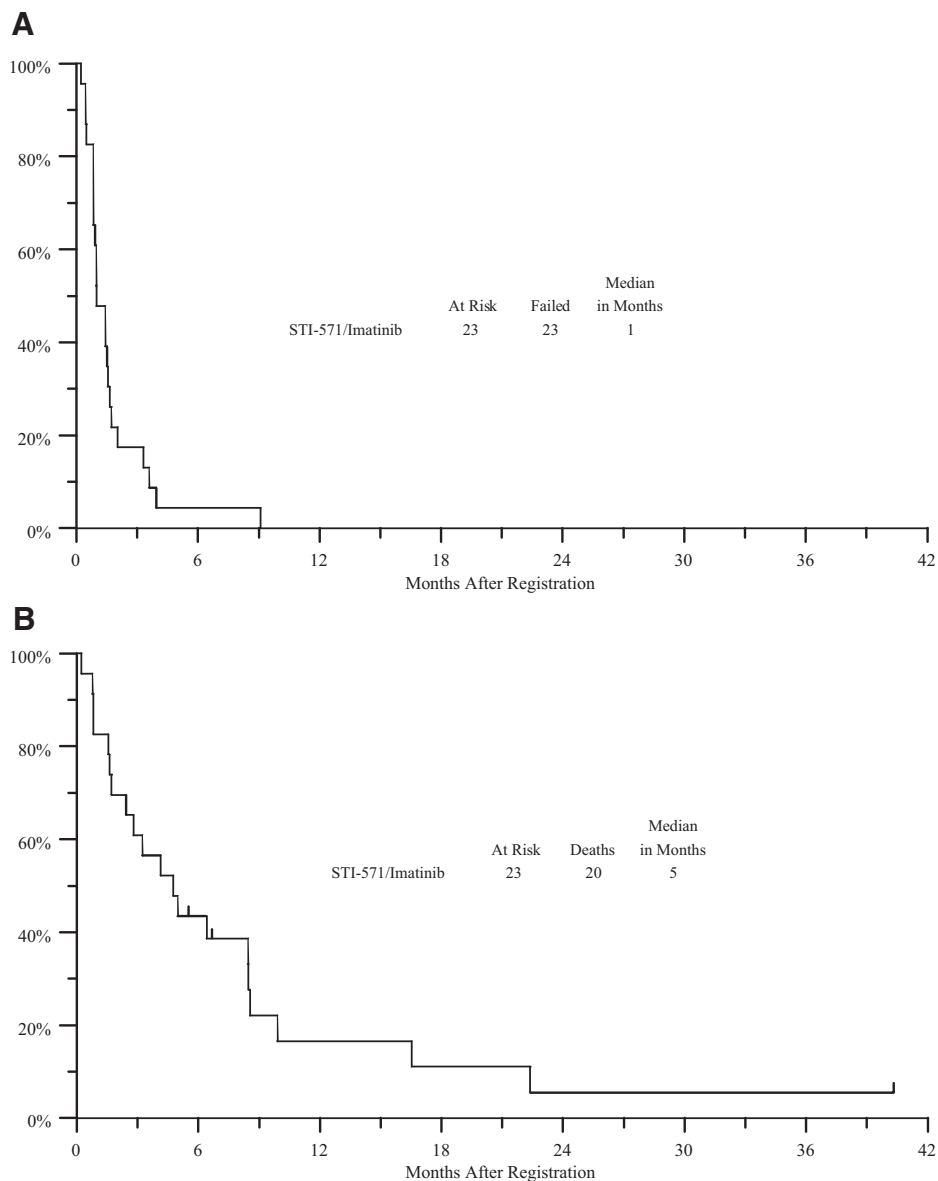
reaction.<sup>21</sup> MCPyV was detected in 77% (n = 30) of MCC as confirmed by sequence analyses of the polymerase chain reaction products. The presence of MCPyV in the majority of MCC tissue specimens strongly indicates a possible role for MCPyV as an etiologic agent in the pathogenesis of MCC.

The significant frequency of distant metastases in MCC has elicited a series of chemotherapy reports based on small numbers of patients.<sup>17,22–27,10–13</sup> Selection of chemotherapy for MCC has usually been patterned after small cell lung cancer treatments because both the lung's Kultchitzky cells and the skin's Merkel cells appear similar by light microscopy and are probably part of the amine precursor uptake and decarboxylation system.<sup>2,23</sup> Although most studies include only a small number of patients, together they have documented frequent though brief responses to several drug combinations. Long-term responses and complete remissions are rarely observed.

A variety of chemotherapy regimens have been employed in patients with metastatic MCC, with a significant frequency of clinical responses. These regimens have included cyclophosphamide, methotrexate and 5-fluorouracil, etoposide and cisplatin, cisplatin plus doxorubicin, and cyclophosphamide, doxorubicin and vinblastine.<sup>17,25,27,28</sup> Accurate estimates of median progression free and overall survival for chemotherapy treatment of metastatic MCC are difficult to ascertain. This is because most reports lump a variety of disease stages and treatment regimens into the same report. Unfortunately, most chemotherapy responses have proven short-lived, although rare long-term remissions have been reported.<sup>10</sup> Because many of the individuals that develop MCC are upwards of 70 years age (mean age of onset is 69), multiagent chemotherapy with anthracyclines and platinum compounds is often poorly tolerated, and must be closely monitored. Thus, identification of novel agents to treat MCC is desirable.

MCC frequently expresses c-KIT CD117, in contrast to a lower incidence of expression in small cell lung cancer.<sup>12–15</sup> Su et al evaluated c-KIT expression in 22 biopsies of MCC.<sup>12</sup> This study found that 21 of 22 MCC biopsies (95%) expressed CD117. Intensity of CD117 expression did not appear to correlate with aggressive behavior. Although the incidence of activating mutations in c-KIT in MCC was not evaluated in this report, its pathogenic role in other malignant neoplasms suggests the possibility of a similar role in MCC.<sup>15</sup>

Imatinib mesylate (Gleevec, formerly STI-571) is a small molecule that has been demonstrated to be a highly selective inhibitor of certain RTK, including (1) Abl and the chimeric BCR-Abl fusion protein found in certain leukemias such as chronic myeloid leukemia; (2) the platelet-derived growth factor receptor; and (3) KIT, the product of the c-KIT proto-oncogene.<sup>29,30</sup> Imatinib inhibits the KIT RTK at an IC50 of approximately 100 nM, which is similar to that required for inhibiting the tyrosine kinase activity associated with BCR-Abl and the platelet-derived growth factor receptor.<sup>31</sup> The selectivity of imatinib is important as it does not affect other members of the type III receptor tyrosine kinase family, such as Flt-3 and the receptor for M-CSF (the product of the c-fms proto-oncogene).<sup>17</sup> Imatinib has been extensively tested in Philadelphia chromosome-positive leukemia patients where the main target is inhibition of the dysregulated kinase activity associated with the chimeric BCR-Abl fusion protein.<sup>32</sup> Additionally, single center and multicenter phase trials have now documented significant activity of imatinib in gastrointestinal stromal tumors, a solid tumor type that usually expresses gain-of-function somatic mutation of the KIT RTK.<sup>33</sup> Our data has demonstrated that imatinib has minimal activity against MCC, despite expression of CD117 (c-KIT) protein. This clinical result has subsequently been explained by molecular studies. MCCs generally fail to express activating mutations in c-KIT.<sup>34,35</sup>



**FIGURE 1.** A, Progression free survival; B, Overall survival.

This was retrospectively confirmed in the tumor of 4 patients with c-KIT expression in the current study. All of these patients had wild-type c-KIT and none of these patients (including 1 with protracted disease stabilization) had activating mutations. A small phase II trial may provide a false-negative result based small sample size and heavily pretreated patients. Because of the low response rate, a relationship to semi-quantitative c-KIT expression could not be evaluated. It is likely that our conclusion of minimal activity in MCC is likely to be correct, based on the lack of activating c-KIT mutations seen in other studies. We would not encourage additional testing of this agent in MCC, unless it is in the setting of c-KIT sequencing and identification of the appropriate activating mutation.

Further efforts are therefore needed to identify agents that are active and tolerable for treatment of patients with this rare, but aggressive skin cancer. It is hoped that the identification of genomic integration of the MCC-associated polyoma virus will provide important clues as to the pathophysiology, as well as aid in the identification of new treatment approaches.<sup>20</sup>

**REFERENCES**

1. Toker C. Trabecular carcinoma of the skin. *Arch Dermatol.* 1972;105:107–110.
2. De Wolff-Peeters C, Marien K, Mebis J, et al. A cutaneous APUDoma or Merkel cell tumor? A morphologically recognizable tumor with a biological and histological malignant aspect in contrast with its clinical behavior. *Cancer.* 1980;46:1810–1816.
3. Gould VE, Moll R, Moll I, et al. Neuroendocrine (Merkel) cells of the skin: hyperplasias, dysplasias, and neoplasms. *Lab Invest.* 1985;52:334–353.
4. Wick MR, Goellner JR, Scheithauer BW, et al. Primary neuroendocrine carcinomas of the skin (Merkel cell tumors). A clinical, histologic, and ultrastructural study of thirteen cases. *Am J Clin Pathol.* 1983;79:6–13.
5. Shaw JH, Rumball E. Merkel cell tumour: clinical behaviour and treatment. *Br J Surg.* 1991;78:138–142.
6. Raaf JH, Urmacher C, Knapper WK, et al. Trabecular (Merkel cell) carcinoma of the skin. Treatment of primary, recurrent, and metastatic disease. *Cancer.* 1986;57:178–182.
7. Yiengpruksawan A, Coit DG, Thaler HT, et al. Merkel cell carcinoma. Prognosis and management. *Arch Surg.* 1991;126:1514–1519.

8. Hitchcock CL, Bland KI, Laney RG, et al. Neuroendocrine (Merkel cell) carcinoma of the skin. Its natural history, diagnosis, and treatment. *Ann Surg*. 1988;207:201–207.
9. Goessling W, McKee PH, Mayer RJ. Merkel cell carcinoma. *J Clin Oncol*. 2002;20:588–598.
10. Goldberg SR, Neifeld JP, Frable WJ. Prognostic value of tumor thickness in patients with Merkel cell carcinoma. *J Surg Oncol*. 2007;95:618–622.
11. Allen PJ, Bowne WB, Jaques DP, et al. Merkel cell carcinoma: prognosis and treatment of patients from a single institution. *J Clin Oncol*. 2005;23:2300–2309.
12. Su LD, Fullen DR, Lowe L, et al. CD117 (KIT receptor) expression in Merkel cell carcinoma. *Am J Dermatopathol*. 2002;24:289–293.
13. Bobos M, Hytiroglou P, Kostopoulos I, et al. Immunohistochemical distinction between merkel cell carcinoma and small cell carcinoma of the lung. *Am J Dermatopathol*. 2006;28:99–104.
14. Strong S, Shalders K, Carr R, et al. KIT receptor (CD117) expression in Merkel cell carcinoma. *Br J Dermatol*. 2004;150:384–385.
15. Feinmesser M, Halpern M, Kaganovsky E, et al. c-kit expression in primary and metastatic merkel cell carcinoma. *Am J Dermatopathol*. 2004;26:458–462.
16. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc*. 1958;53:457–481.
17. Tai PT, Yu E, Winkquist E, et al. Chemotherapy in neuroendocrine/Merkel cell carcinoma of the skin: case series and review of 204 cases. *J Clin Oncol*. 2000;18:2493–2499.
18. Tai PT, Yu E, Tonita J, et al. Merkel cell carcinoma of the skin. *J Cutan Med Surg*. 2000;4:186–195.
19. Skelton HG, Smith KJ, Hitchcock CL, et al. Merkel cell carcinoma: analysis of clinical, histologic, and immunohistologic features of 132 cases with relation to survival. *J Am Acad Dermatol*. 1997;37:734–739.
20. Feng H, Shuda M, Chang Y, et al. Clonal integration of a polyomavirus in human Merkel cell carcinoma. *Science*. 2008;319:1096–1100.
21. Kassem A, Schopflin A, Diaz C, et al. Frequent detection of Merkel cell polyomavirus in human Merkel cell carcinomas and identification of a unique deletion in the VP1 gene. *Cancer Res*. 2008;68:5009–5013.
22. Crown J, Lipzstein R, Cohen S, et al. Chemotherapy of metastatic Merkel cell cancer. *Cancer Invest*. 1991;9:129–132.
23. Feun LG, Savaraj N, Legha SS, et al. Chemotherapy for metastatic Merkel cell carcinoma. Review of the M. D. Anderson Hospital's experience. *Cancer*. 1988;62:683–685.
24. Fenig E, Brenner B, Njuguna E, et al. Oral etoposide for Merkel cell carcinoma in patients previously treated with intravenous etoposide. *Am J Clin Oncol*. 2000;23:65–67.
25. Voog E, Biron P, Martin JP, et al. Chemotherapy for patients with locally advanced or metastatic Merkel cell carcinoma. *Cancer*. 1999;85:2589–2595.
26. Bajetta E, Rimassa L, Carnaghi C, et al. 5-Fluorouracil, dacarbazine, and epirubicin in the treatment of patients with neuroendocrine tumors. *Cancer*. 1998;83:372–378.
27. Fenig E, Lurie H, Sulkes A. The use of cyclophosphamide, methotrexate, and 5-fluorouracil in the treatment of Merkel cell carcinoma. *Am J Clin Oncol*. 1993;16:54–57.
28. Poulsen M, Rischin D, Walpole E, et al. High-risk Merkel cell carcinoma of the skin treated with synchronous carboplatin/etoposide and radiation: a Trans-Tasman Radiation Oncology Group Study—TROG 96:07. *J Clin Oncol*. 2003;21:4371–4376.
29. Druker BJ, Sawyers CL, Kantarjian H, et al. Activity of a specific inhibitor of the BCR-ABL tyrosine kinase in the blast crisis of chronic myeloid leukemia and acute lymphoblastic leukemia with the Philadelphia chromosome. *N Engl J Med*. 2001;344:1038–1042.
30. Savage DG, Antman KH. Imatinib mesylate—a new oral targeted therapy. *N Engl J Med*. 2002;346:683–693.
31. Druker BJ, Tamura S, Buchdunger E, et al. Effects of a selective inhibitor of the Abl tyrosine kinase on the growth of Bcr-Abl positive cells. *Nat Med*. 1996;2:561–566.
32. O'Brien SG, Guilhot F, Larson RA, et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. *N Engl J Med*. 2003;348:994–1004.
33. Demetri GD, von Mehren M, Blanke CD, et al. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. *N Engl J Med*. 2002;347:472–480.
34. Swick BL, Ravdel L, Fitzpatrick JE, et al. Merkel cell carcinoma: evaluation of KIT (CD117) expression and failure to demonstrate activating mutations in the C-KIT proto-oncogene - implications for treatment with imatinib mesylate. *J Cutan Pathol*. 2007;34:324–329.
35. Kartha RV, Sundram UN. Silent mutations in KIT and PDGFRA and coexpression of receptors with SCF and PDGFA in Merkel cell carcinoma: implications for tyrosine kinase-based tumorigenesis. *Mod Pathol*. 2008;21:96–104.