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c-kit (CD117) Expression in Human Tumors and its Prognostic Value: An Immunohistochemical Analysis

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Abstract c-kit functions as a tyrosine kinase receptor and represents a target for small molecule kinase inhibitors. The expression pattern for c-kit was studied in different human tumor types to their correlation with prognosis. Paraffin-embedded tumor tissues from 282 patients were analyzed immunohistochemically for c-kit expression. Survival and follow-up data were available from 192/282 (68%) patients. c-kit immunopositivity was found in 62/282 (22%) cases. c-kit expression was found in 14/83 (17%) colorectal cancers, in 13/62 (21%) breast cancers, in 7/20 sarcomas (35%), in 5/14 (36%) renal cell carcinomas, in 2/12 ovarian cancers (17%) and in 2/12 (17%) hepatocellular carcinomas. We found no significant correlation between c-kit expression and prognosis although a trend to a worse prognosis in patients with c-kit positive tumors could be observed. Expression of c-kit was found in tumor samples with varying intensities and infrequently.

Keywords c-kit · Imatinib · Immunohistochemistry · Prognosis · Solid tumors · Tyrosine kinases

Abbreviations

GIST	gastrointestinal stromal tumors
PDGF	platelet-derived growth factor
PKCθ	protein kinase C theta

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Introduction

The proto-oncogene c-Kit (CD117) encodes a transmembrane tyrosine kinase receptor related to the platelet-derived growth factor PDGF/CSF-1 (c-fms) receptor subfamily [1]. c-kit is involved in the growth and development of mast cells and of premature stromal cell or interstitial cell of Cajal [2]. Kit activation normally occur when two adjacent receptors are brought together by a homodimer ligand. A series of events occurs to activate cell-signaling cascades that are important in the regulation of proliferation, apoptosis, adhesion, and differentiation in several cell types [3, 4]. It plays an important role in the development of multiple cell types, including hematopoietic cells, germ cells, and melanocytes [4, 5].

KIT expression has been detected in a variety of different tumor entities such as gastrointestinal stromal tumors (GIST), malignant melanoma, breast and lung cancer, sarcoma and mastocytosis [6–11]. In GIST, the frequency

of KIT positivity is so high (90% to 95%) that immunohistochemical KIT detection is considered a prerequisite for the histologic diagnosis of GISTs [12]. Further markers in GISTs are CD34 (60–70%) and smooth muscle actin (30–40%, usually focal and weak staining) but KIT is established as the most specific and sensitive diagnostic marker [13]. New promising markers were recently discovered to increase the accuracy of diagnosis. The expression of protein kinase C theta (PKCθ) has been identified and found to be specific for GIST [14]. DOG1 was highly specific for GIST, but exceptional DOG1-positive other mesenchymal tumors were found [15]. Further, keratin-positive GIST should also be considered as GIST can be positive for both KIT and cytokeratin [16]. In these cases, c-kit mutation analysis can be helpful.

The KIT protein is normally activated through binding to its ligand (stem cell factor). The neoplasms often harbor KIT activating mutations that result in constitutive ligand-independent KIT phosphorylation and downstream activation [17].

KIT alterations in malignant tumors are of high interest because KIT is one of the targets of tyrosine kinase inhibitors (eg imatinib mesylate, sunitinib, nilotinib, dasatinib). Imatinib mesylate is a selective inhibitor of certain tyrosine kinases, including ABL, BCR-ABL, ARG, KIT, and the platelet-derived growth factor receptors (PDGFRs) [18]. Imatinib has initially been shown to be effective in the treatment of chronic myeloid leukemia, where it targets the BCR-ABL fusion protein and the treatment of GIST where it targets the c-kit tyrosine kinase [19–23]. It is hoped that other KIT-positive tumors may also benefit from therapy with kinase inhibitors directed against it. It has been observed that the response rate may be particularly high in KIT-expressing tumors that also harbor activating KIT mutations [24].

The studies available until now about prognosis show controversy results regarding c-kit expression. While numerous clinical studies showed that cancer patients with either over-expression and/or mutations of c-Kit in their clinical samples have significantly poor prognosis, lower survival rates and show resistance to chemotherapy [25–30] other studies found no prognostic significance of c-kit expression [31–33].

As c-Kit is now a potential target for site-specific therapy in certain solid tumors, the identification of over-expression by standard immunohistochemical techniques would be a significant scientific advance in our understanding of expression pattern in solid tumors.

Therefore, the aim of this study was to investigate the frequency of c-kit protein expression and relevance on prognosis in various tumor types. In the present study, we stained several human tumor types for the KIT protein using immunohistochemistry.

Patients and Methods

Patients and Tissues

This study was approved by the Ethic committee of the University Hospital Freiburg, Germany. We reviewed, under informed consent, formalin-fixed, paraffin-embedded tissue sections of different tumor types that were resected from patients who were treated at the Tumor Biology Center Freiburg, Germany between 2001 and 2004. A total of 282 patients with a mean age of 61.3 years were evaluated retrospectively. Follow-up and survival data were available from 192 of 282 patients (68%). The tumor material was available from the institutes of Pathology, were the initial diagnosis was made. All cases were histological classified according to the World Health Organization criteria. All slides from all tumors were reviewed by one of two pathologists (M. K. and H.-E. S.) to define the histological grade (well (G1), moderately (G2) and poorly (G3) differentiated) and the histological tumor type.

Table 1 shows the number of cases and histological classification of the tumor subgroups.

Immunohistochemistry

Sections from formalin-fixed and paraffin-embedded tumor tissue were processed for immunohistochemistry using a polyclonal rabbit anti-human c-KIT antibody (DAKO, Cat. No. A4502) at a 1:100 dilution. For the purposes of our present study, we used the rabbit polyclonal antibody A4502, which has shown consistent performance even against a low background and because it is the most widely used KIT antibody and because it is the antibody specified for CD117 (c-Kit) testing in the large co-operative clinical trials involving imatinib. The sections were incubated with primary antibody for 1 h. For the detection of the primary antibody, a commercially available detection kit (ChemMate™ Detection Kit, Alkaline Phosphatase/RED, Rabbit/Mouse, DAKO) was used with the DakoCytomation TechMate™ and Autostainer Instruments were used following the manufacturer's instruction. Finally, the reaction is visualized by a RED chromogen. Appropriate positive and negative controls were used throughout the testing process. Mast cells were uses as internal positive control. Tumor cells that showed cytoplasmic and/or membrane immunoreactivity for c-kit were considered positive. As a negative control, the same procedure was followed, but with the substitution of an unrelated rabbit antibody instead of the c-kit antibody. Counterstaining was performed in hematoxylin solution. For each tissue sample, the percentage of positive cells was estimated and the staining intensity was recorded semiquantitatively from 0 (nega-

Table 1 Patient characteristics, c-kit expression and univariate analysis (Kaplan–Meier survival and log rank statistics) in human tumors

Tumor type	Cases (n)	Kaplan–Meier Log rank *P*-values[a]	c-kit expression all n (%)	c-kit expression (n)		
				+	++	+++
Colorectal carcinoma	83	0.353	14 (17 %)	9	5	
Breast carcinoma	62	0.078	13 (21 %)	7	6	
Sarcoma[b]	20	0.065	7 (35 %)[c]	4	1	2
Renal cell carcinoma	14	0.870	5 (36 %)	2	1	2
Ovarian carcinoma	12	0.133	2 (17 %)	2		
Hepatocellular carcinoma	12	0.892	2 (17 %)		2	
Others		n.s.				
Non-Hodgkin's lymphoma	9		0			
Small cell lung carcinoma	3		2	1	1	
Papillary thyroid carcinoma	2		1	1		
Urinary bladder, transitional-cell carcinoma	5		0			
Carcinoma of unknown primary +	20		1	1		
Esophagus, adenocarcinoma	7		2	1	1	
Gastrointestinal stromal tumors	2		2			2
Squamous cell carcinoma of larynx	3		0			
Pleuramesothelioma	2		0			
Seminoma	2		1			1
Neuroendocrine carcinoma	4		3		1	2
Stomach, adenocarcinoma	3		0			
Prostate, adenocarcinoma	3		0			
Non-small cell lung cancer	5		2	2		
Pancreas, adenocarcinoma	2		0			
Melanoma	7		5	4		1
Total:	79		19/79 (24%)			
Total:	**282**		**62/282 (22%)**	**34/62 (54%)**	**18/62 (29%)**	**10/62 (16%)**

+ Carcinoma of unknown primary includes 15 adenocarcinoma, 3 poorly differentiated carcinoma and 2 neuroendocrine carcinoma

+ weak; ++ medium; +++ strong c-kit expression

[a] from 192 patients were follow-up data were available

[b] The sarcoma include the following subtypes: 1 schwannoma, 3 leiomyosarcomas, 2 hemangioendothelioma, 1 hemangiopericytoma, 4 chrondrosarcomas, 1 fibrosarcoma, 2 sarcomas not otherwise specified (NOS), 3 liposarcoma, 1 myofibroblastic sarcoma, 1 histiocytoma of the parotid gland, 1 breast angiosarcoma

[c] Positive c-kit sarcoma were: 2 chondrosarcoma, 2 leiomyosarcoma, 1 myofibroblastic sarcoma, 1 histiocytoma of the parotid gland, 1 breast angiosarcoma

tive), + (weak), ++ (medium), +++ (strong). Staining results were interpreted by a single pathologist (MK) who was blinded from the clinical data.

Statistical Analysis

Clinical data were obtained by reviewing the charts and contacting the physicians in charge. Overall survival was defined as the period of time from initial diagnosis to death or last contact, that is, date of last follow-up visit. Survival analysis was determined according to the Kaplan–Meier method and statistical significance of the differences in survival distribution was evaluated by the log-rank test. The a priori level of significance was set at $P<0.05$. All statistical analyses were carried out using SPSS® software, version 15.0 (SPSS Inc. Chicago, IL, USA).

Results

The histopathological features and c-kit immunostaining of the 282 patients are reported in Table 1. The patients' ages at diagnosis ranged from 19 to 84 years, with a mean age of 61.3 years. From all patients 136 were female and 146 male.

The tumor types included 83 colorectal cancer samples, 62 breast cancer, 20 sarcoma (1 schwannoma, 3 leiomyosarcomas, 2 hemangioendothelioma, 1 hemangiopericytoma, 4 chrondrosarcomas, 1 fibrosarcoma, 2 sarcomas not otherwise specified (NOS), 3 liposarcoma, 1 myofibroblastic sarcoma, 1 histiocytoma of the parotid gland, 1 breast angiosarcoma), 14 renal cell carcinoma, 12 ovarian cancer, 12 hepatocellular carcinoma and 79 others. Survival and follow-up data were available from 192/282 (68%) patients. The median follow-up is 27 months (range, 2–271 months). 18 of the patients were alive and 174 died during the follow-up.

Positive staining for c-kit was observed in 62 of 282 analysed patients (22%), whereas 220/282 (78%) cases were negative. Positive slides showed clear cytoplasmic staining including membrane staining in at least 10% of all tumor cells (Fig. 1a–c). In every staining session c-kit-positive mast cells was used as a positive control. c-kit expression was found in 14/83 (17%) colorectal cancer, in 13/62 (21%) breast cancer, in 7/20 sarcoma (35%, namely 2 chondrosarcomas, 2 leiomyosarcomas, 1 myofibroblastic sarcoma, 1 histiocytoma of the parotid gland, 1 breast angiosarcoma), in 5/14 (36%) renal cell carcinoma, in 2/12 ovarian cancer (17%), in 2/12 (17%) hepatocellular carcinoma, in 5/7 (71%) melanoma and in 19/79 (24%) others. A strong (+++) expression of c-kit was found in 2 sarcomas, 2 renal cell carcinomas, 2 carcinoids, 1 seminoma, 1 melanoma and 2 GISTs. Of all 62 cases positive for c-kit, a strong expression was found in 10/62 (16%), c-kit medium (++) expression in 18/62 (29%) and c-kit low (+) reactivity was found in 34/62 (54%). c-kit expression and intensity according to tumor type are shown in Table 1.

Cumulative survival curves were calculated according to the Kaplan-Meier method, and differences in survival were assessed using the log-rank test (Table 1). There was no association between c-kit expression and patient survival although a trend toward a worse prognosis of c-kit-positive tumors could be observed, especially in breast carcinoma and sarcoma (Table 1, Fig. 2). Comparison of c-Kit expression and patients' outcome using log-rank tests showed that c-Kit was not a significant prognostic indicator in patients with colorectal carcinoma (p=0.353), breast carcinoma (p=0.078), sarcomas (p=0.065), renal cell carcinoma (p=0.870), ovarian carcinoma (p=0.133) and hepatocellular carcinoma (p=0.892) (Table 1, Fig. 2).

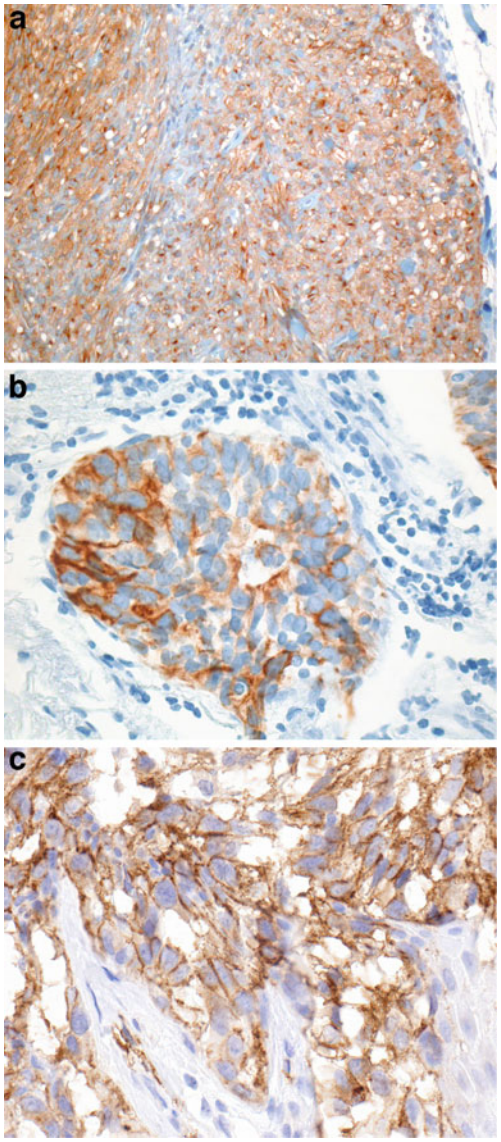

Fig. 1 Immunohistochemical staining using a polyclonal rabbit antibody against c-kit in different tumor types. **a** Positive c-kit staining of tumor cells in a gastrointestinal stromal tumor (original magnification 50×). **b** Positive c-kit staining of tumor cells in a thymic carcinoma (original magnification 200×). **c** Positive c-kit staining of tumor cells in melanoma (original magnification 200×)

Discussion

c-kit expression plays a pathogenic role in a number of malignancies besides GIST, namely breast carcinomas, germ cell tumors, colon carcinoma, some subtypes of sarcoma, melanoma, ovarian and small cell lung carcinoma [34–36]. Inhibition of the c-kit and the PDGFR pathway with low-molecular-weight kinase inhibitors resulted in clinical benefits in patients with GIST [23] and dermatofibrosarcoma protuberans [37]. However, recent trials indicate that a relevant response to imatinib was only achieved in patients with activating mutations and in most of these cases the role of c-KIT in the neoplasia is not completely understood. The response to kinase inhibitors (eg imatinib) may not be driven exclusively by the KIT expression level. Studies have shown that not all KIT-expressing solid and hematological malignancies will benefit from imatinib therapy [38–40]. They indicate that the response rate may

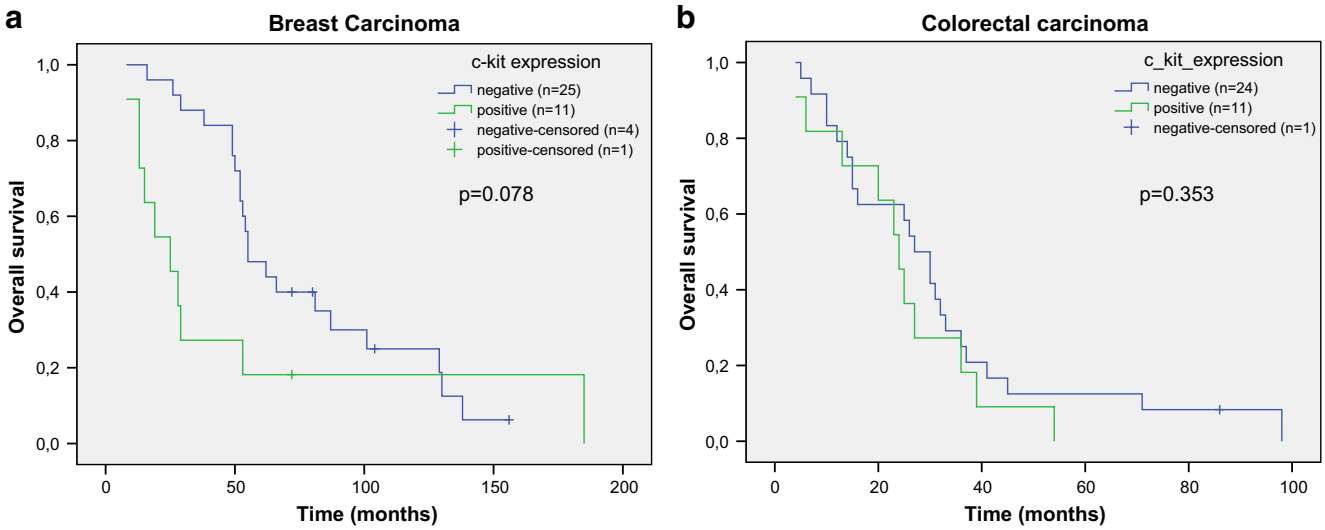

Fig. 2 Survival analysis (Kaplan–Meier model) of c-kit-positive versus c-KIT-negative tumors. **a** breast carcinoma. Note that there is only a trend toward a better overall survival ($p=0.078$) **b** colorectal carcinoma

depend on the presence of KIT mutations in the tumor and potentially also on the location and type of mutation as well as the interaction with other signal pathways. Imatinib or sunitinib therapy of KIT-positive GISTs represents an example of a rationally targeted cancer therapy requiring immunohistochemical tumor analysis to identify patients most amenable to such therapy. Thereby, tumors with exon 11 mutations respond better than those tumors with exon 9 mutations, whereas the response rate is minimal in tumors without mutations [24].

In a recent study by Heinrich et al. 186 patients with solid and hematologic malignancies were treated with imatinib. Thereby, patients with dermatofibrosarcoma protuberans, aggressive fibromatosis, hypereosinophilic syndrome, and myeloproliferative disorders had a clinical benefit from imatinib therapy. The other tumor types had no response to imatinib treatment. There was no clear relationship between expression or activation of wild-type imatinib-sensitive tyrosine kinases and clinical response [41].

In our study, a large series of solid tumors was analyzed immunohistochemically for c-kit expression. All together, the expression rate of c-kit besides sarcoma, renal cell carcinoma and melanoma seems low compared to GIST in solid tumors. Tumors with activating KIT or PDGFRA mutations are potential targets for imatinib and other selective tyrosine kinase inhibitors. Together with the low prevalence of mutations in KIT-expressing tumors, this would suggest a relatively low proportion of patients who might benefit from imatinib therapy subsequent to KIT activation. In a study by Sihto et al. KIT mutations were uncommon in most tumors beside GIST [42].

Nevertheless the relatively high c-kit expression in sarcomas, melanoma, renal cell carcinoma, seminoma and neuroendocrine carcinoma is intriguing and deserves further evaluation on a greater number of samples to be representative. The number of probes from breast and colon carcinoma analyzed are more elevated and could be quite representative showing a c-kit expression in around 20% of this cases but none of them at high level. The c-kit analyses in other tumor entities suggests an expression rate around 25% some of them at high level but this group is very heterogeneous and might not be absolutely representative deserving further analysis on a greater number of probes from each tumor entity.

In our study we found no significant correlation between c-kit expression and prognosis although a trend toward a worse prognosis in c-kit positive tumors was seen in breast carcinoma and sarcoma. Concerning c-kit expression and prognosis the available data are controversial. In a recent study by Charpin et al. [28] c-Kit expression in patients with breast carcinomas correlated with a poor patient outcome while a other study found that a loss of the c-kit expression is associated with an advanced stage of breast cancer [32].

In conclusion, our study supports and considerably extends previous studies analyzing c-kit expression in solid tumors showing that a strong c-kit expression is rarely observed in solid tumors analyzed so far. Nevertheless we observed a consistent expression even at high level in some entities like sarcoma, renal cell carcinoma, melanoma, seminoma and neuroendocrine tumors that deserves further evaluation. Furthermore we should be conscious that the expression level of growth factor receptors not always

predicts the activity of kinase inhibitors in the complex context of intracellular signal pathways. Screening of tumor samples on the expression of specific growth factor receptors is nonetheless still very relevant since it gives us valuable informations on the characteristics of tumors helping us to better understand the complex interactions of signal transduction pathways and guide us in the development of more specific therapies.

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