

Recurrent Squamous Cell Carcinoma of the Skin – a Rare Side Effect of nilotinib

Ali W. Rizvi, DO¹; Adriani Cherico, MD¹; Thejus Jayakrishnan, MD¹; Lisa Pawelski, MD³; Prerna Mewawalla, MD²

¹Department of Medicine; ²Division of Medical Oncology, Allegheny Health Network, Pittsburgh, PA; ³Dermatologic Care, Inc., Pittsburgh, PA



Introduction

- Chronic myeloid leukemia (CML) is a type of myeloproliferative neoplasm and linked to translocation between chromosomes 9 and 22 resulting in the over expression of BCR-ABL gene, which increases cell proliferation
- Tyrosine kinase inhibitors (TKI) are the treatment of choice for CML as it selectively inhibits BCR-ABL
- Patients on TKIs have been shown to be at higher risk for secondary malignancies

Methodology

- Case review through electronic medical record
- Extensive literature review

Case Presentation

- 79-year-old male with CML who was on imatinib therapy for 10 years experienced disease progression to accelerated phase with WBC > 150,000 (7% blasts)
- Patient required hospitalization and therapy transition to dasatinib then subsequently to nilotinib due to dasatinib's cardiopulmonary side effects
- Bone marrow biopsy showed hypercellular marrow with myeloid hyperplasia
- Fluorescent in situ hybridization (FISH) confirmed BCR/ABL gene in 52.6% of cells
- Patient developed multiple skin lesions that were confirmed as squamous cell carcinoma (5 lesions over 7 months), requiring removal via Mohs micro-surgery
- Current disease status is complete cytogenetic response (CCyR) with major molecular response (MMR)

Discussion

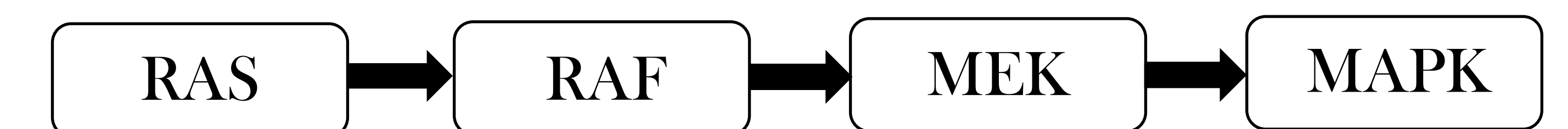
- Nilotinib is a 2nd generation TKI that is known to have adverse reactions including vascular events (especially in patients with increased risk for cardiovascular disease) (1), psoriasis (2), thrombocytopenia, myalgia, headache (3), QT prolongation and hyperbilirubinemia (5)
- Development of secondary malignancies (SM) while on TKI over a 10-year period found that gastrointestinal, nose and throat cancers were more common in these patients (6)
- Interestingly, the most common nonhematologic adverse reaction with TKI involves the skin. These have been documented as skin pruritis and rash as well as occasional benign papillomas and panniculitis (4).
- The association of nonmelanotic skin cancers with nilotinib is rare as seen in this case and two others (see table 1 below)

Authors	Skin cancer history	Primary cancer	Duration of therapy before diagnosis	SCC characteristic	# of lesions	Treatment of SCC	Recurrence	Outcome
Crain, et al.	Nonmelanoma (SCC/BCC?)	CML (PHL +)	1 week	Keratoacanthoma-type SCC Well differentiated SCC	10	Electrodesiccation & curettage	Yes, after 1 month; repeat electrodesiccation & curettage	Good; Alternative CML therapy
Peters, et al.	Intraepithelial carcinoma; BCC (excised 2 years prior to Nilotinib)	CML (PHL +)	6 months	Well differentiated SCC	9	Systemic retinoid	None	Good; continued Nilotinib
Our paper	SCC BCC	CML (PHL +)	7 months	Well differentiated SCC	5	Mohs micrographic surgery/shaving	None	Good; continued Nilotinib

Conclusion

It is proposed that nilotinib induced BRAF inhibition may cause paradoxical activation of oncogenic Ras pathway in pre-disposed patients as ours, however further clinical investigation is recommended

In normal tissue:



In SCC tissue (already oncogenic RAS present):

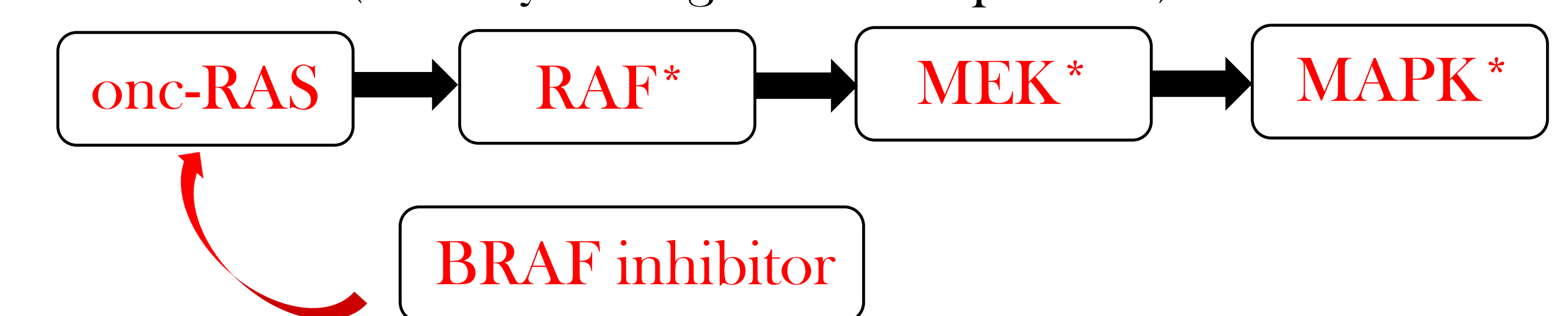


Figure 1. Outlining the pathway of activation of MAPK in normal tissue and SCC tissue

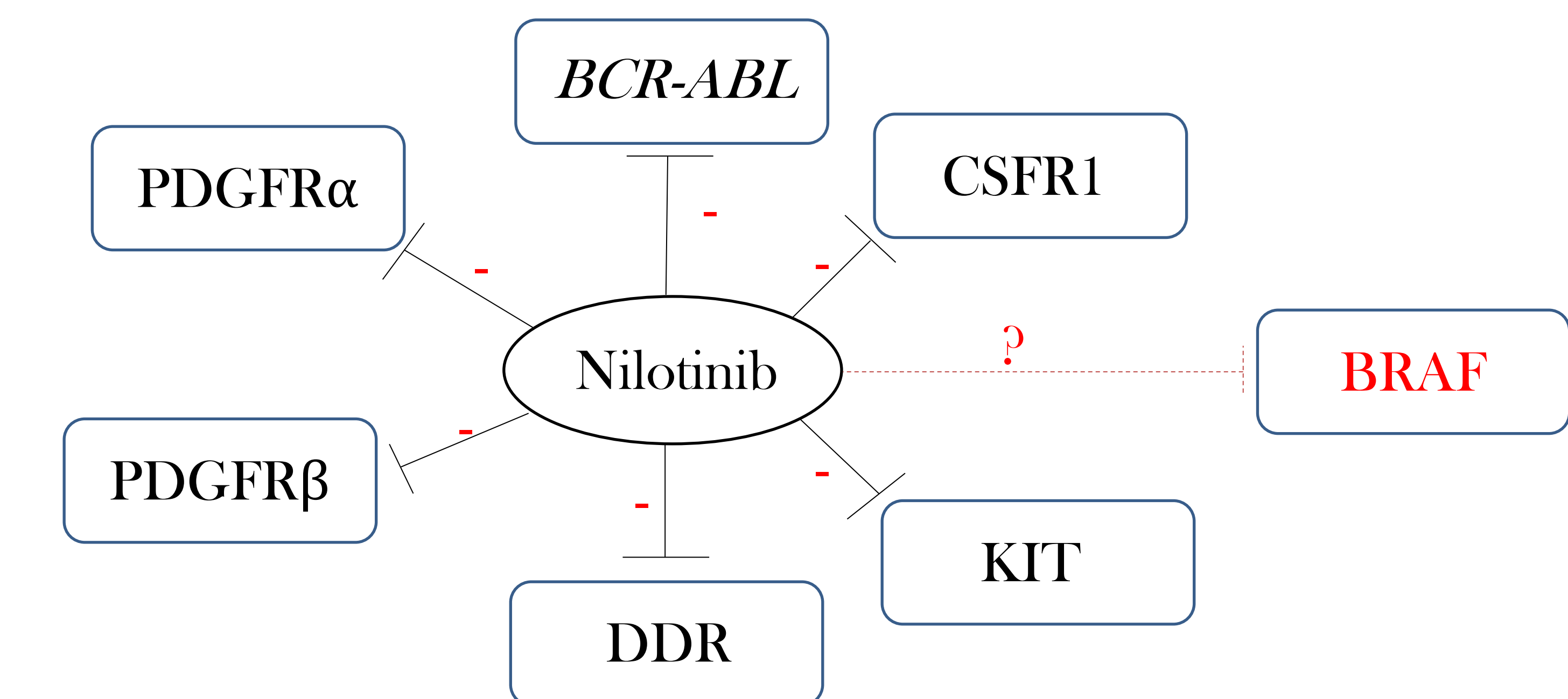


Figure 2. Mechanism of action of nilotinib

References

- Eskazan AE. Vascular Adverse Events During Long-term Nilotinib Therapy in Patients With Chronic Myeloid Leukemia. *Clin Lymphoma Myeloma Leuk.* 2017 Dec;17(12):e63-e64. doi: 10.1016/j.clml.2017.07.010. Epub 2017 Aug 1. PMID: 2883067
- Nagai T, Karakawa M, Komine M, Muroi K, Ohtsuki M, Ozawa K. Development of psoriasis in a patient with chronic myelogenous leukaemia during nilotinib treatment. *Eur J Haematol.* 2013 Sep;91(3):270-2. doi: 10.1111/ijh.12153. Epub 2013 Jun 28. PMID: 23734955.
- Hussain S, Usman Shaikh M. Response and Adverse Effects of Nilotinib in Imatinib-resistant Chronic Myeloid Leukemia Patients: Data From a Developing Country. *Clin Ther.* 2015 Nov 1;37(11):2449-57. doi: 10.1016/j.clinthera.2015.08.026. Epub 2015 Sep 26. PMID: 26409289.
- Delgado L, Giraudier S, Ortonne N, Zehou O, Cordonnier C, Hulín A, Chosidow O, Tulliez M, Valeyrie-Allanore L. Adverse cutaneous reactions to the new second-generation tyrosine kinase inhibitors (dasatinib, nilotinib) in chronic myeloid leukemia. *J Am Acad Dermatol.* 2013 Nov;69(5):839-840. doi: 10.1016/j.jaad.2013.07.025. PMID: 24124828
- Kim MK, Cho HS, Bae YK, Lee KH, Chung HS, Lee SY, Hyun MS. Nilotinib-induced hyperbilirubinemia: is it a negligible adverse event? *Leuk Res.* 2009 Sep;33(9):e159-61. doi: 10.1016/j.leukres.2009.04.013. Epub 2009 Jun 2. PMID: 19493567.
- Gunnarsson N, Stenke L, Höglund M, Sandin F, Björkholm M, Dreimane A, Lambe M, Markevårn B, Olsson-Strömberg U, Richter J, Wadenvik H, Wallvik J, Sjölander A. Second malignancies following treatment of chronic myeloid leukaemia in the tyrosine kinase inhibitor era. *Br J Haematol.* 2015 Jun;169(5):683-8. doi: 10.1111/bjh.13346. Epub 2015 Mar 27. PMID: 25817799.