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^{18}F-labelled fluorodeoxyglucose–positron emission tomography (FDG–PET) heterogeneity of response is prognostic in dabrafenib treated BRAF mutant metastatic melanoma ☆

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Abstract ***Background:*** Little is known about the prevalence and clinical significance of heterogeneity of positron emission tomography with ^{18}F-labelled fluorodeoxyglucose–positron emission tomography (FDG–PET) response. We aim to determine the prevalence, and clinicopathologic correlates of intra-patient heterogeneity of FDG–PET response in metastatic melanoma treated with dabrafenib, and to determine whether heterogeneity predicts clinical outcome.

Methods: Patients with BRAF mutant metastatic melanoma and $\geqslant 2$ FDG avid lesions treated on the Phase I trial of dabrafenib at a single institution ($n = 23$) were included. FDG–PET response was assessed by comparing baseline PET scans with scans at day 15. A heterogeneous response was defined as responding and new or metabolically progressing lesion(s) in a patient, or >10% of lesions with a stable metabolic response and responding lesions in a patient.

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Results: Six (26%) patients had a heterogeneous PET response. The median time to progression (TTP) was 7.4 months (95% confidence interval (CI): 6.5–8.3) for PET homogeneous responders and 3.0 months (95% CI: 0.6–5.4) for PET heterogeneous responders. There were no homogeneous non-responders. Age, BRAF mutation genotype, dose, and lactate dehydrogenase, did not predict for heterogeneity of PET response. Heterogeneity did not correlate with tumour response. Lung metastases were more likely to respond than other visceral metastatic sites.

Conclusions: Heterogeneous FDG–PET responses are common in metastatic melanoma treated with dabrafenib, and heterogeneity is associated with a shorter TTP. FDG–PET heterogeneity may predict molecular heterogeneity, and FDG–PET directed biopsies may facilitate investigation into mechanisms of resistance to signal pathway inhibitors.

1. Introduction

Melanoma shows marked genetic instability and intratumoural molecular heterogeneity.[1,2] Genetic divergence occurs during the clonal evolution of melanoma and in some cases multiple coexisting metastases can arise from genetically different tumour clones.[3] Indeed, BRAF mutant and wildtype tumour cells have been shown to be present in a single melanoma.[2,4] Intra-patient tumour heterogeneity may have treatment implications particularly in the era of targeted therapies which act to inhibit specific molecular targets, such as mutated kinases.[5]

Approximately 50% of melanomas have activation of the mitogen-activated protein kinase (MAPK) pathway due to mutations in the proto-oncogene BRAF.[6,7] The potent ATP-competitive BRAF inhibitors, vemurafenib (PLX4032) and dabrafenib (GSK2118436), have proven efficacy in the treatment of BRAF-mutant metastatic melanoma, with response rates of 50% and improved progression-free and overall survival compared with dacarbazine.[8–11]

Positron emission tomography (PET) with ^{18}F-labelled fluorodeoxyglucose (FDG) and more recently combined PET and computed tomography (CT) have been used to monitor response in systemic cancer therapy.[12] An early reduction in FDG uptake after commencing systemic treatment in lymphoma,[13–15] breast cancer,[16] non-small cell lung cancer (NSCLC)[17] and gastrointestinal stromal tumours[18] correlates with response and, in some cases, survival. Heterogeneity of PET radiopharmaceutical uptake has been shown to reflect differences in tumour biology and may be predictive for response to treatment.[19,20]

FDG–PET is an early marker of biological response in BRAF mutant metastatic melanoma treated with vemurafenib, reflecting rapid inhibition of tumour metabolism.[21] However no relationship was observed between PET response and Response Evaluation Criteria in Solid Tumors (RECIST) response or progression free survival.[21]

We observed intra-patient heterogeneity of response and progression on CT scans during the phase 1 study of dabrafenib. Changes in FDG uptake correlate with BRAF inhibitor melanoma cell line sensitivity,[22] and together with evidence of molecular heterogeneity in solid tumours,[1,2,23] we hypothesise that a heterogeneous PET response may act as a surrogate marker for populations of tumour cells that are less sensitive to dabrafenib.

The aim of this study is to determine if intra-patient heterogeneity of PET response occurs in BRAF mutant metastatic melanoma treated with dabrafenib, and if heterogeneity predicts the time to progression (TTP) and/or overall survival (OS), or is correlated with clinicopathologic features of metastatic melanoma.

2. Patients and methods

2.1. Patients

The study was undertaken at Westmead Hospital with Human Ethics Review Committee's approval and informed patient consent. Patients enrolled on the dose escalation (part 1) of the BRF112680 Phase I trial of dabrafenib at Westmead Hospital were considered for analysis. Eligibility criteria included presence of BRAF mutant metastatic melanoma, available baseline and day 15 PET scans, and at least 2 FDG avid lesions on the baseline PET scan. Patients were allowed dose escalation to the recommended phase 2 dose (150 mg twice daily) after both PET scans were performed. All included patients were $\geqslant$18 years of age, had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1 and adequate organ function.

2.2. PET scanning

All patients were imaged on dedicated PET/CT systems. All patients fasted for at least 6 h before radiopharmaceutical injection and their blood glucose level did not exceed 7 mmol/L. Whole body PET imaging from vertex to toes started between 60 and 75 min after administration of a mean dose of 360 MBq 18-F FDG (range 317–464 MBq). A 'low dose' CT without intravenous contrast administration was acquired concurrently for attenuation correction and anatomical localisation. Baseline and day 15 PET scans were performed on the