Novel treatment (new drug/intervention; established drug/procedure in new situation)

Good clinical and radiological response to BRAF inhibitor in patient with metastatic thin melanoma

Keith Ian Quintyne,¹ Shirley Baker,¹ Fintan Wallis,² Rajnish Gupta^{1,3}

¹Medical Oncology Department, Mid-Western Regional Hospital, Limerick, Ireland;

²Radiology Department, Mid-Western Regional Hospital, Limerick, Ireland;

³Stokes Research Institute, University of Limerick, Limerick, Ireland

Correspondence to Dr Keith Ian Quintyne, keithi.quintyne@hse.ie

Summary

The authors herein report the case of a 32-year-old man with advancing metastatic malignant melanoma, who has progressed through all previous lines of therapy, presenting with ongoing respiratory tract symptoms of exertional shortness of breath and cough. CT restaging confirmed clinical findings of deteriorating pulmonary disease; histological review revealed V600E BRAF mutation. He was started on targeted biological therapy with BRAF inhibitor GSK2118436, and is having a good clinical and radiological response without significant lasting toxicity.

BACKGROUND

Malignant melanoma remains a very aggressive cancer to manage, with no clear standard therapy available.¹ Dacarbazine has long been considered a reference drug for many years.² Molecular targeted therapies offer promise in management of malignant melanoma, due to exploded greater knowledge of melanoma cell signalling and immunological responses; most specific to malignant melanoma is the activating mutation in the BRAF oncogene,³ that is seen in approximately 40–55% of patients with malignant melanoma.⁴

We herein report the case of a Caucasian man of Irish extraction who developed progressive metastatic melanoma and proceeded with biological therapy with the BRAF inhibitor GSK2118436 following the detection of BRAF mutation.

CASE PRESENTATION

A Caucasian teacher in his early 30s, who is a lifetime non-smoker and non-sunbather, with no family history of malignancy, who gives a history of a left shoulder malignant melanoma that was superficial spreading, Clark level III, Breslow thickness 0.8 mm, mitotic rate was 2 per 10 high power fields, brisk infiltrating lymphocytes and presence of regression without ulceration and lymphovascular or perineural invasion. It was staged as a T_{1A}NxM0 melanoma for which he had undergone a wide local excision in August 2005, and had further excision in September 2005, to insure clear margins, and no adjuvant therapy was offered.

In June 2010, he was reviewed for a persistent non-productive cough, and clinical examination revealed no obvious cause for this. CT staging revealed a speculated mass in his right mid-zone, for which he underwent a right thoracotomy and middle lobectomy and confirmed malignant melanoma. Postoperative recuperation was uneventful and restaging with positron-emission tomography/CT staging was performed and revealed no obvious residual disease, and he was initiated on biological therapy with interferon. In December 2010, the patient was reviewed

and restaging revealed the new development of bilateral pulmonary metastases, he was then started on palliative biological therapy with ipilimumab in the outpatient setting and tolerated four cycles without need for blood products, growth factor support or treatment delay. Restaging on completion of therapy again showed progressive disease and collapse of his right lung, with interim development of respiratory symptoms of shortness of breath, dry cough and right-sided chest pain.

In May 2011, he underwent five fractions of palliative radiotherapy without significant improvement in his clinical picture. His thoracotomy specimen was sent for BRAF mutation testing and revealed that his tumour had a V600E BRAF mutation.

In June 2011, with an Eastern Co-operative Oncology Group (ECOG) performance status (PS) of 2, intermittent domiciliary oxygen and nocturnal methadone for symptom relief was needed. He started on GSK2118436 BRAF inhibitor. Serial CT scanning over the initial 8 weeks showed regression of his bilateral pulmonary metastases with re-inflation of his right lung and improvement in his ECOG PS from 2 to 0/1. These are shown in the figures 1 and 2.

Figure 1 CT – 30 June 2011 – Pre-exposure to BRAF inhibitor.

Figure 2 CT– 18 August 2011 – Postexposure to BRAF inhibitor – 8 weeks.

OUTCOME AND FOLLOW-UP

The patient has tolerated his therapy without side effects for 23 weeks. Ultimately his quality of life has improved, and he has been able to maintain wean himself off his methadone, play golf three times a week and attend his outpatients' appointments.

DISCUSSION

The diagnosis of malignant melanoma has always been associated with a grim prognosis; but with the efforts made by Breslow about 40 years ago, stratifying patients with melanoma become possible; he noted that patients could be categorised based on the thickness of their primary lesion, with lesions less than 0.76 mm (thin melanomas) being associated with a very good outcome;⁵ this consequently led to derivation in current use in clinical dermatology, Breslow thickness. The American Joint Committee on Cancer (AJCC) have reproduced these results and expanded on these, and have selected a cut-off of 1.0 mm. The primary tumour in this case was 0.8 mm, which by the AJCC and Breslow criteria should have been associated with a better overall outcome, but unfortunately falls into the 5% category, that despite good features still succumb to their disease, and the disease-free survival falls from 100% to 70%.⁶

Other pathological features such as the presence of regression within the tumour have been debated, as it may result in an underestimation of the true Breslow thickness; however recent reviews have shown that it is not a significant prognostic factor for patients with melanoma, and should not be used as a guide in clinical decision-making, as it does not impact on disease-free survival or overall survival.⁷ For this case, regression was noted, and no other features such as lymphovascular invasion was appreciated, as this can be a power predictor of worst overall survival in patients who have evidence of regression apparent in their primary tumours.⁸

Melanoma is considered to be one of the malignancies with great metastatic potential.⁹ The therapeutic option which confers the best outcome remains adequate surgical resection,¹⁰ however options for advanced or metastatic disease remain refractory to current chemotherapeutic therapies (which include dacarbazine, taxanes, fotemustine or others, cytokines

or combinations) and are often associated with a very poor prognosis with median survival rate of 6 months.¹¹

Given these bleak figures, it remains important to be able to balance actively treating a patient with advanced disease and limiting toxicity and any ill effects on quality of life.

Advances have been made in the general understanding of cancer biology, cell signalling and immunological responses, with therapeutic strategies that target RAF proteins, specifically BRAF, which is part of the serine/threonine kinase proteins. For malignant melanoma, BRAF mutation can be noted in 40–55% of cases,⁴ and is normally associated tumorigenesis and its progression and ultimately a poor prognosis.⁹ Of interest, there is an insignificant trend towards longer median overall survival from time of diagnosis for wild-type BRAF versus mutant-type BRAF melanoma tumours;¹² this is driven by current speculation within the published literature that BRAF mutated melanoma tumours have a more aggressive biology with poor chemotherapy-sensitivity, results in a more unfavourable outcome when compared with BRAF wild-type melanoma tumours.¹³ Within recent times several newer agents including GSK2118436 and vemurafenib have become available on compassionate grounds outside of the clinical trial setting; they exert their therapeutic effect by inhibition of RAF kinase activity, consequently nullifying hyperactivation that can occur with mutations in BRAF oncogene, whereby activation can take place due to presence of aspartic acid or the fact for only phosphorylation is required for activation.⁹ In BRAF mutated melanoma tumours, levels of RAS activation are noted to be reduced, and these newer agents bind to BRAF (V600E) monomers and inhibit their activity; this results in tumour-specific inhibition of the ERK signalling pathway.¹⁴

For this case GSK2118436 was offered to the patient, which is a highly potent, reversible and selective ATP competitive BRAF inhibitor; it displays dose-dependent inhibition of MEK and ERK phosphorylation in mutant BRAF cells.¹⁵ For GSK2118436 the mode of action is through a persistent competitive inhibition of ATP binding and highly selective for the inhibition of BRAFV600E with a selectivity that is 375-fold for BRAF600VE panels of almost 300 protein and lipid kinases, except in eight known kinases, for which the IC₅₀ values of GSK2118436 were less than 100nM.¹⁶ GSK2118436 also reduces phosphorylation of ERK in BRAFV600E mutated cell lines at consistent levels (half maximal inhibitory concentration (IC₅₀) values 3–120 nM), while cell lines from wild-type BRAF were less sensitive (IC₅₀ values >900 nM).¹⁶ In BRAF mutated cell lines, this agent was not to induce a concentration-dependent cell cycle arrest in G₀/G₁ phase at 24 h followed by apoptosis.¹⁶ It was also noted to have negligible effects on proliferation and non-proliferating normal human umbilical vein endothelial cells, potentially alluding to limited toxicity in normal human cells.¹⁶

It has been well tolerated in the outpatient setting without need for blood products or growth factor support for the patient in this report. Common side effects experienced with the use of BRAF inhibitors include arthralgias, rash, fatigue, alopecia, photosensitivity, nausea, diarrhoea and the development of squamous-cell carcinomas.¹³ It was noted that approximately two-fifth of patients required dose modifications due to grade 3 or more toxicity.^{13 15} Specifically for GSK2118436, in a preliminary phase II trial of 92 patients, approximately 87% of cohort had experienced at least one

adverse event (AE) of any grade, but these were primarily grade 1 or 2.¹⁶ The most commonly experienced AE, that was seen in more than 15% of subjects was arthralgia, fatigue, headache, hyperkeratosis, nausea and fatigue, with only seven patients (8%) experiencing grade 4 adverse event; none of the subjects involved experiencing any fatal adverse events.¹⁶ But for this case none of the mentioned toxicities have been experienced with his exposure to GSK2118436.

Most concerning for patients on BRAF inhibitors, is the development of squamous cell carcinomas, which was observed in 15–30% of patients.^{15 16} The biology behind these lesions is not clear, but most postulate that given there are RAS mutations in pre-existing lesions that may experience paradoxical activation of the mitogen-activated protein kinase pathway consequently leading to squamous cell carcinomas, possibly due to downstream alterations in BRAF due to exposure of BRAF inhibitors.¹⁷ The patient has not developed any squamous cell carcinomas to date.

In its preliminary testing in data from a phase III trial of 675 patients with malignant melanoma, vemurafenib was administered as single agent therapy and a survival advantage was appreciated in overall survival and progression-free survival, with an objective response rate of 48.4%.¹⁸ Further reports released about BRIM3 have noted at the interim 3 month analysis, that there was a 63% reduction in risk of death and 74% reduction in disease progression.¹⁹

Learning points

- ▶ The patient had clinical, histological and radiological features of markedly migrating metastatic melanoma.
- ▶ The patient was an ideal candidate for targeted therapy with BRAF inhibitor, as it appears safe without significant toxicity.
- ▶ Insured and improved patient's quality of life, without significant toxicity from intervention.
- ▶ Its early days in therapy for this patient, but it is important to document the outcome

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Competing interests None.

Patient consent Obtained.

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