CASE REPORT

Resolution of lung adenocarcinoma after discontinuation of ibrutinib

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Accepted 2 July 2016

SUMMARY

The new capability to generate mimicking chemical analogues and perform mass screenings of candidate drugs has been tested on B-cell receptor signalling, a driver of B-cell malignancies. These efforts have identified ibrutinib as a potent inhibitor of Bruton's tyrosine kinase. As the clinical use of ibrutinib increases, continued vigilant monitoring for rare adverse events is prudent, including the development of secondary malignancies. To date, the most common reported secondary malignancy is non-melanoma skin cancer; however, we present a case of secondary primary lung adenocarcinoma becoming clinically apparent shortly after initiating therapy with ibrutinib. Our patient had a sudden regression of the tumour with discontinuance of ibrutinib, and based on our understanding of paradoxical tumour growth caused by tyrosine kinase inhibitors it is our hypothesis that the complex multikinase activity of ibrutinib may stimulate tumour growth by targeting a subset of protein kinases critical for growth in some cancer cells.

BACKGROUND

Ibrutinib is a potent inhibitor of Bruton's tyrosine kinase (BTK). Ibrutinib demonstrated efficacy in several clinical trials for B-cell lymphoma. As a targeted oral agent, with a contending lower toxicity profile, ibrutinib is especially advantageous in older patients with relapsed disease. As the clinical use of ibrutinib increases, continued vigilant monitoring for rare adverse events is prudent, including the development of secondary malignancies. To date, the most common reported secondary malignancy is non-melanoma skin cancer, but other malignancies have also been described including non-small cell adenocarcinoma.[1] We also present a case of secondary primary lung adenocarcinoma becoming clinically apparent shortly after initiating therapy with ibrutinib. However, to the best of our knowledge this is the first reported case with a sudden regression of the tumour with discontinuance of ibrutinib.

Based on our understanding of paradoxical tumour growth caused by tyrosine kinase inhibitors it is our hypothesis that the complex multikinase activity of ibrutinib may stimulate tumour growth by targeting a subset of protein kinases critical for growth in some cancer cells. Further studies are needed to understand the clinical implications of the wide off-target effects of kinase inhibitors and to identify underlying mechanisms of secondary tumour growth associated with ibrutinib to help guide the development of BTK inhibitors.

CASE PRESENTATION

A 75-year-old male patient, with a 10 pack-year cigarette smoking history (cessation in 1975) presented for management of relapsed mantle cell lymphoma (MCL). His medical history was significant for coronary artery disease post three stents and gastro-oesophageal reflux disease. The patient's previous restaging showed new lymph node enlargement and after consultation he consented to therapy with ibrutinib (560 mg per os daily) and rituximab (protocol 2013-0090). At the time of consent, a review of his systems was negative, physical examination was normal, lungs were clear to auscultation, a lymph node survey was negative except for a palpable groin lymph node and the patient was given a list of all strong CYP3A inhibitors to avoid while on the study.

Therapy was tolerated, but the patient developed a grade 1 skin lesion on his scalp, forehead and a rash on his lower extremities. Multiple punch biopsies were consistent with a hypersensitity reaction to an internal antigen, suggesting a drug-related eruption; still, treatment was not interrupted or modified following the clinical trial protocol.

Four-and-a-half months after beginning his therapy (after five cycles of ibrutinib) the patient presented to the emergency room with a productive cough and haemoptysis (small amount blood-tinged sputum), fever ($T_{max,}$ 38.3°C), lethargy and chest pain.

INVESTIGATIONS

A CT pulmonary angiogram was performed to rule out emergent conditions which revealed an interval change described as a mass-like consolidation in the medial aspect of the right lower lobe believed to be suspicious for malignancy or an infectious process when compared to a CT scan performed 1 month earlier (figure 1A, B). Routine laboratory results were within normal limits and the patient indicated that he avoided strong CYP3A inhibitors.

OUTCOME AND FOLLOW-UP

The patient was admitted and his treatment with ibrutinib and rituximab was placed on hold pending a CT-guided biopsy of the right lung mass and restaging studies. At the time of biopsy, 3 weeks after discontinuing ibrutinib, the mass had regressed from 6 cm (figure 1B) to ~2.5 cm in maximal dimension (figure 1C).

The biopsy of the right hilar azygoesophageal lesion revealed adenocarcinoma (figure 2A, B), further classified as an invasive adenocarcinoma, acinar type, without lymphocytic infiltration.

To cite: Khashab T, Loghavi S, Konoplev SN, *et al*. *BMJ Case Rep* Published online: [*please include* Day Month Year] doi:10.1136/bcr-2016-215342

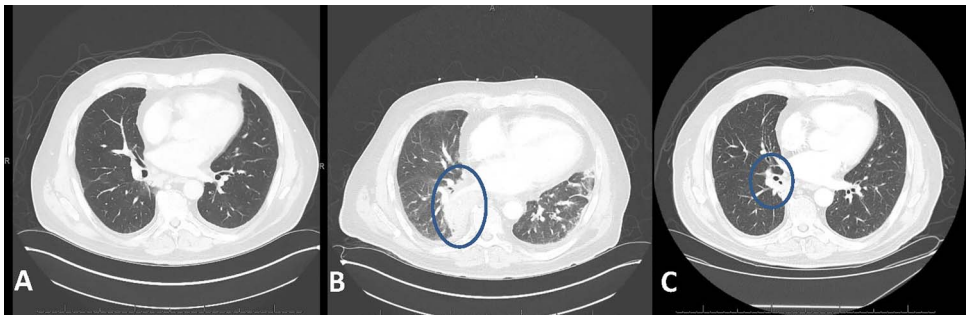

Figure 1 CT scan 4 weeks before presenting to the ER (A) CT scan 1 day after discontinuing ibrutinib, the lesion was 6 cm in maximal dimension (poor inspiratory effort) (B). Interval CT scan 3 weeks later showing the consolidated opacity along the medial right lower lobe with significant decrease in size (C).

However, the CT-guided biopsy did not yield enough sample for further molecular and immunohistochemistry studies. Endobronchial ultrasound for mediastinal staging revealed non-diagnostic results and after consultation with a multidisciplinary group the patient elected to receive radiation therapy for his lung adenocarcinoma. Restaging studies after radiation therapy revealed stable MCL disease and the patient did not restart treatment with ibrutinib or any other regimen.

DISCUSSION

The offered mechanism of action of ibrutinib is as a selective inhibitor of BTK, forming a covalent bond with the cysteine residue in the BTK active site, resulting in inhibition of BTK enzymatic activity. However, at therapeutic doses, the activity of ibrutinib is not limited to selective action on BTK, as in vitro and animal model studies reveal action on multiple protein kinases such as ITK, CSK and others.[2] In fact, the inherent promiscuity of kinase inhibitors has led to the repurposing of many drugs for use in other malignancies because targeting multiple redundant signalling pathways is clinically efficacious. Demonstrating the potential benefit of ibrutinib's off-target effects, our colleagues, Gao *et al*[3] showed that 3 of 39 lung adenocarcinoma cell lines harbouring EGFR mutations were sensitive at clinically relevant doses to ibrutinib. While targeting multiple pathways can be advantageous, it may also lead to unintended side effects. Based on our understanding of paradoxical tumour growth caused by other tyrosine kinase inhibitors it is our hypothesis that the complex multikinase activity of ibrutinib may stimulate tumour growth by targeting a subset of protein kinases critical for growth in some cancer cells. When signalling is affected, regulatory loops are often disrupted, which can cause upregulation of signalling pathways that could result in the unintended tumour growth, and make a possibly undetected tumour clinically apparent. This may especially be evident in lung adenocarcinoma cells which lack BTK receptors, the intended target of ibrutinib.

Spontaneous rapid regression of lung adenocarcinoma is highly unlikely. The dramatic partial regression of the lung lesion in our patient after discontinuing therapy strongly suggests a role for ibrutinib in the progression of the tumour, and, while we do not know the exact mechanism, a relationship is strongly suggested based on our understanding of the phenomenon of secondary tumour growth with tyrosine kinase inhibitors. For example, the BRAF kinase inhibitor vemurafenib has been used in the treatment of late stage melanoma, and secondary primary malignancies are common with vemurafenib therapy, such as well-differentiated cutaneous squamous cell tumours and other malignancies.[4–6] Callahan *et al* reported a patient with stage IV melanoma, who shortly after treatment with vemurafenib developed an unrecognised NRAS-mutant chronic myelomonocytic leukaemia. Additional studies and analysis revealed a white cell count (WCC) population with high extracellular signal-regulated kinase (ERK) expression. Discontinuing treatment led to a decrease in the WCC with a concurrent reduction in ERK expression. A rechallenge with a lower dose of vemurafenib also stimulated a WCC rise, confirming the association.[7] An ERK-activated tumour proliferation driven by vemurafenib was also described in a patient with melanoma who developed chronic lymphocytic leukaemia (CLL) (RAS wild type). The investigators suggest a different mechanism of B-cell receptor/spleen tyrosine kinase (SYK)-activated RAS based on their in vitro studies and xenograft models.[8] The increase in risk of a secondary malignancy is not limited to vemurafenib, as other kinase inhibitors have also been implicated.

In clinical practice, the multikinase RAF inhibitor sorafenib has also been associated with the development of cutaneous

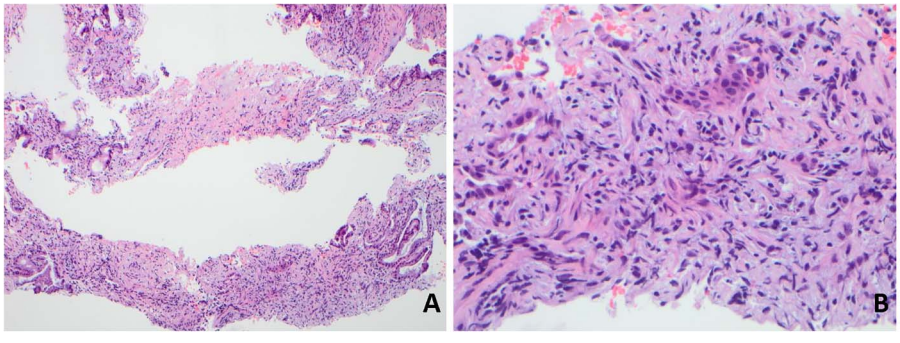

Figure 2 The alveolar lung parenchyma is infiltrated by irregularly shaped glandular structures composed predominantly of cuboidal cells with hyperchromatic nuclei. Prominent desmoplastic stromal reaction is noted (H&E, A: ×100; B: ×400).

squamous cell tumours and other tumours.[6 9] Mellema *et al*[10] reported a significant tumour flare of a KRAS-mutated non-small cell lung cancer (NSCLC) after treatment with sorafenib and hypothesised that the association is related to the paradoxical activation of the RAS-MAPK pathway. This hypothesis is based on a study by Callahan *et al*[7] who demonstrated substantial tumour growth after treatment with RAF inhibitors through paradoxical MAPK activation (wild-type MAPK pathway or non-RAF-MAPK pathway mutations). The types of tumours and mechanisms of paradoxical growth with use of tyrosine kinase inhibiters are distinct. However, similar to some of the cases presented our patient had a sudden regression of the tumour with the discontinuance of ibrutinib, and the wide off-target effects of ibrutinib strongly suggest a potential role in clinical progression of the adenocarcinoma.

In the case outlined, the patient's lymphoma responded to treatment with ibrutinib but with unintended growth of the secondary malignancy. Characterising the mechanisms behind this unintended tumour growth will aid in the development of more effective BTK inhibitors, and will help guide physicians in managing complications by potentially using combination therapies to ameliorate the adverse effects without discontinuing therapy. To illustrate this clinical point, in vitro studies by Callahan *et al*[7] found that RAF inhibitor-induced ERK activation was diminished by the addition of a MEK inhibitor. Their findings demonstrate the importance in understanding the mechanisms of unintended secondary cancer progression, which may provide potential therapeutic strategies that can be used in clinical practice. Without further studies it is unknown if the observed side effect is from an unknown or unpredicted target or from the combination effect of the modulation of several target kinases. Future clinical studies would benefit from comparing the side effects, including secondary tumour growth between ibrutinib, a first-generation BTK inhibitor, and newer second-generation specific BTK inhibitors like acalabrutinib (ACP-196) which is already in clinical trials. Acalabrutinib demonstrates more selective BTK binding without inhibiting many other tyrosine kinases like EGFR and ITK, and it is believed that this will result in a better side effect profile.[11]

Vigilant long-term monitoring of patients taking the first-generation BTK inhibitor ibrutinib, especially those with risk factors for lung cancer is necessary to improve the risk assessment. Additionally, further studies to identify the underlying mechanisms of secondary tumour growth associated with ibrutinib are needed to help guide the development of BTK inhibitors.

Learning points

- The most common pulmonary adverse events with ibrutinib, a Bruton's tyrosine kinase inhibitor, are upper respiratory tract infections, pneumonia, cough and dyspnoea. Secondary primary malignancies have occurred, most commonly skin cancers; while other malignancies have been reported, which are rare and not well described in the literature.
- We present a patient who developed a clinically apparent lung adenocarcinoma shortly after the initiation of treatment with ibrutinib; there was rapid regression of his tumour shortly after discontinuing therapy.
- Other tyrosine kinases inhibitors have been implicated in paradoxical tumour growth, but to the best of our knowledge this is the first reported case of ibrutinib therapy and its association with a non-small cell lung carcinoma followed by spontaneous tumour resolution after discontinuance of the drug.
- Ibrutinib also targets other tyrosine kinases at therapeutic doses; therefore its inherent promiscuity may drive tumour growth.
- Clinicians should be aware and vigilant to the phenomenon of secondary tumour growth when treating patients with novel targeted cancer therapies.

Contributors TK collected the case material, interpreted data and wrote the manuscript. SL generated pathological data and wrote the manuscript. SNK generated pathological data and wrote the manuscript. FS designed the study, interpreted data and wrote the manuscript.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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Unexpected outcome (positive or negative) including adverse drug reactions