CASE REPORT

Imatinib in neurofibromatosis type 2

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SUMMARY

A 30-year-old man with a 10-year history of neurofibromatosis type 2 (NF-2) and minimal hearing in his left ear, presented with rapidly progressive disease and risk of total hearing loss. He was started on imatinib and achieved stable disease for 4 months, after which the drug was ceased due to toxicity. He was then treated with bevacizumab for 8 months with a best response of stable disease.

BACKGROUND

Neurofibromatosis type 2 (NF-2) is a rare disease with limited systemic treatment options, representing an unmet need. Potential drugs would need to target the underlying molecular pathways and be well tolerated given the chronicity of this disease. Imatinib is a tyrosine kinase inhibitor which targets c-kit, and fits both these criteria. Randomised clinical trials are unlikely to be conducted in this rare disease and phase 0 trials are likely the way forward. We describe to our knowledge, the first case report of the use of imatinib for patients with NF-2.

CASE PRESENTATION

A 30-year-old mechanic with no other significant medical history was seen at the medical oncology clinic for consideration of systemic therapy for progressive NF-2. He was first diagnosed with NF-2 in 2003, aged 28, when he presented with a 6-month history of forehead numbness, left ear pain, diplopia on left gaze, reduced hearing on the right, and loss of balance. MRI revealed a 4×3 cm left cerebellopontine angle mass extending into the region of Meckel's cave, left cavernous sinus and left middle cranial fossa, representing neuromas of the fifth and eighth cranial nerves. There was also a 3.5×3 cm right cerebellopontine angle mass extending into the right internal acoustic meatus, consistent with a right eighth cranial nerve neuroma.

He underwent stereotactic craniotomy and excision of the left trigeminal schwannoma on 12 August 2003, and resection of the right cerebellopontine tumour via a right translabyrinth approach on 28 October 2003, with no postoperative complications. A year later, there was no evidence of the right acoustic neuroma, but a residual left acoustic neuroma (15×16×19 mm) and a small residual nodule (1 cm) in the site of the resected left trigeminal schwannoma in the region of Meckel's cave was noted. Audiometry showed mild to moderately severe sensorineural hearing loss in the left ear and profound loss in the right.

He was lost to follow-up intermittently until 2009. MRI on 11 September 2009 showed bilateral

vestibular schwannomas (28×27 mm on the left, 18×14 mm on the right), as well as a residual left trigeminal schwannoma. Serial imaging indicated that they had increased around 10% since August 2008. There were no spinal cord abnormalities. Audiometry in July 2010 showed mild to moderately severe sensorineural hearing loss in the left ear and profound loss in the right, which had not changed significantly since 2007.

In late 2010, he noticed increasing ataxia and hearing loss. MRI on 28 October 2010 showed that the right schwannoma now measured 28×19×35 mm, a relatively rapid increase by around 60% over 12 months. The left-sided lesion measured 31×33×33 mm, corresponding to an interval enlargement of 20–25%. The left trigeminal lesion measured 17×12 mm, which was unchanged. There was also a cervical spine C5/6 small focus of enhancement representing tumour of dorsal nerve root, and a similar lesion in C6/7. There were multiple intrathecal extramedullary nodules involving the lower thoracic and lumbar region of spine. During this period, he had visited multiple institutions without any definitive management plan and was becoming increasingly frustrated.

TREATMENT

He was initially seen at our centre on 10 February 2011. Given the relatively rapid increase in size of his multiple neuromas, we considered that he was at a risk of total hearing loss and brainstem compression and would require urgent treatment. Surgery would carry the risk of complete hearing loss and damage to the left facial nerve, and was unacceptable to him and his family at that point in time. We were able to obtain imatinib on compassionate grounds (Novartis Australia Pty Ltd); after full disclosure and informed consent, he was administered a dose of 400 mg daily for 2 weeks and thereafter, 400 mg twice a day. Baseline MRI on 9 March 2011 prior to the starting of imatinib showed that the right cerebellopontine mass had increased further by around 30%.

OUTCOME AND FOLLOW-UP

He was reviewed every 2 weeks and over the first 4 weeks, he felt that his gait, hearing and visual symptoms had improved subjectively since starting imatinib. No side effects were noted other than mild light-headedness lasting 10 min after taking the drug. Follow-up MRI on 10 May 2011 showed stable appearance of bilateral vestibular schwannomas and left trigeminal schwannoma. Serial monthly auditory evoked brainstem responses were stable. A single serum imatinib concentration was measured on 27 May 2011 which showed that a

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therapeutic concentration of 2187 ng/mL had been achieved (therapeutic level >1100). In July 2011, he was found to have a causative mutation in the NF-2 gene.

Approximately 4 months after the starting of imatinib, he developed grades 1 and 2 nausea, vomiting and abdominal pain and increased unsteadiness, headache and hearing loss and stopped imatinib of his own accord. MRI on 9 August 2011 showed that the left vestibular schwannoma had slightly increased in size by 3–4 mm, although the right vestibular and left trigeminal schwannoma remained relatively stable in size and appearance.

Subsequently, he started the therapy with bevacizumab on 9 September 2011. A follow-up MRI 2 months later showed a 30×33 mm left vestibular schwannoma, and a 32×20 mm right schwannoma, both slightly smaller in size. The left trigeminal schwannoma remained stable and there was decreased mass effect and decompression of the ventricles. Audiometry on 8 November 2011 remained unchanged. He continued on bevacizumab for a total of 8 months, with a best response of stable disease, but reported subjective improvement in hearing. There was no toxicity from treatment.

DISCUSSION

In vitro data on the activity of imatinib and nilotinib against NF-2 cells^{1 2} suggest that c-kit is a useful target; given that imatinib is an effective inhibitor of c-kit, among other targets, we reasoned that this drug might be suitable for our patient. Since survival in NF-2 is often measured in years and the bulk of symptoms are caused by slow-growing tumours,³ chronic treatment is ideal. As a result, the long-term tolerability of tyrosine kinase inhibitors⁴ makes them a potentially suitable treatment. However, our patient was unusual in that he developed toxicities after only 4 months of treatment. Although stable disease was the best objective response recorded, the patient did report some subjective improvement in symptoms.

Most of the evidence for NF-2 therapy is provided by level IV studies based on the vascular endothelial growth factor inhibitor bevacizumab.⁵ However, randomised trials in this rare disease are unlikely to ever be conducted, so phase 0 studies to explore the pharmacokinetics and pharmacodynamics of targeted therapies may be a suitable approach. Alternatively, adaptive phase II trials, or small multiarm trials,⁶ could be used to seek regulatory approvals for new therapies. Systemic therapy remains a challenging problem in NF-2 and there is a need for

better understanding of the underlying signal transduction pathways that could lead to utilisation of well-tolerated targeted therapy. To our knowledge, this is the first case report of the use of imatinib for a patient with NF-2.

Learning points

- ▶ Neurofibromatosis type 2 (NF-2) is a rare disease with limited systemic treatment options.
- ▶ Potential drugs should target the underlying signal transduction pathways, such as c-kit, and be well tolerated, given the chronicity of this disease. Imatinib is a tyrosine kinase inhibitor which fits both these criteria.
- ▶ Level A evidence is unlikely to ever be available for these orphan diseases and hence we propose that phase 0 studies are a suitable approach.

Contributors Both authors have contributed to the article's conception, acquisition of data, drafting the article and revising it critically. They have approved the final version for submission.

Competing interests None.

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