

NICE Technology Appraisal – Trabectedin for advanced soft tissue sarcoma

Personal Statement from Roger Wilson

In April 2000, following surgery for a primary tumour in 1999 (diagnosed as leiomyosarcoma) and then for lymphatic metastasis earlier in the year, I was diagnosed with an unresectable tumour in the groin. I was told that any treatment would be with palliative intent.

I was offered the choice of doxorubicin (the standard treatment) or of entering a clinical trial of first-line chemotherapy (EORTC 62971) which was comparing doxorubicin against two experimental schedules of ifosfamide. I chose the trial and was randomised to the high dose ifosfamide arm – 9mg/m² delivered intravenously over 72 hours with mesna.

A CT scan after the second cycle (June 2000) indicated a response, which was confirmed after six cycles. In September I was told I was in 'remission' but was also made aware that the median time to progression was 15 weeks. Earlier discussion with my oncologist had already told me that median survival untreated was around 9 months and that long term survival from chemotherapy alone was around 3%.

My response has proved durable and just how unusual that is was revealed by the trial report, finally published in 2007. The trial was stopped at the interim review as it was clear that the hypothesis (a 10% improvement with ifosfamide) would not be proved. 14 patients were surviving at 4 years from the 322 treated on the trial (4.3%). Median time to progression and overall survival were consistent with historic data.

No-one can be certain why I survived, even though I have had a later localised recurrence during which my tumours were re-diagnosed to myxoid fibrosarcoma. The probability is that my lymphatic metastasis, itself unusual, had the characteristics of a local recurrence rather than the characteristics of systemic disease. As no-one has distinguished such differential characteristics this can only be pure guesswork.

This experience qualifies me to comment on the situation facing patients entering an end-of-life pathway with this disease.

In common with many patients with advanced sarcoma I was asymptomatic and in excellent shape at the time of starting the first-line treatment. Four months of therapy left me tired and suffering from the anticipated side effects (hair loss, nausea etc) though I had avoided any problems with my blood. I was 54, reasonably fit, certainly capable of caring for myself, of walking several miles (if more slowly than previously) and I was still at work (I was home based).

Had I progressed the only treatment option before me would have been doxorubicin as second-line therapy. There is plenty of evidence that resistance to one of dox and ifos predicts resistance to the other. There were no further options should dox have failed, as would have been anticipated by my doctors.

The dilemma of whether to accept further treatment should I have relapsed was one which occupied my mind a lot. Yes, a response was positive, but a further relapse would have been devastating. The thought of another four months of chemotherapy with all the side effects and (in this case) the prospect of cardiac side effects (my family has a history of heart disease) followed by a rapid decline to death, was not a good prospect. That decline might come sooner with no treatment but living for some months without the too-familiar side effects would have been attractive.

This internal discussion began to abate after about two years but still lingers within me, nearly ten years on.

This has been ten years with few indications that any new treatments would be forthcoming. Trabectedin is the only exception until very recently, and the newer therapies entering trials today will not receive marketing authorisation for some years, if at all. I welcome the availability of trabectedin. It holds out the promise that extended life of a good quality can be achieved by patients with refractory disease, and for those that fail the treatment early it is not too onerous. One of the keys to this is that there is no cross-resistance with dox/ifos, meaning that the accelerated failure of treatment which many patients face when taking a second-line chemotherapy, is not a factor which has to be considered.

I look forward to trabectedin entering trials as a first-line therapy for which I believe it will become valued. However, first it must enter standard practice in second-line, in which it will offer life and extend hope to the relatively small numbers of patients who each year face advanced soft tissue sarcomas.