PERSONAL STATEMENT BY Dr ANAND SHARMA

Health technology Appraisal
Oxaliplatin and capecitabine for the adjuvant treatment of colorectal cancer

Introduction

Thank you for the opportunity to present my view to the appraisal committee. I was diagnosed with rectal cancer at the age of 33. It was a Dukes C2 tumour, T3N9M0 or stage III in terms of grade. I have now been in full remission for 17 months. The opinions that I express are my own as someone that is living with a diagnosis of colorectal cancer and should not to be regarded as representative of any particular group or organisation. It is, out of necessity, a very personal account.

My treatment

Prior to surgery I was entered into a clinical trial [because I had a fixed tumour] with a combination of therapies including

1. Irinotecan, i.v. weekly for 5 weeks
2. Capecitabine, oral, daily for 5 weeks
3. Radiotherapy, 25 doses, given over 5 weeks.

I then had a curative resection with a loop ileostomy.

After 6 weeks I began a 24-week bolus 5FU/FA regimen.

Subsequently I have had a reversal of the ileostomy. I am currently well and have been back at work full time for 4 months.

How I got my treatment

Soon after my diagnosis I embarked on a crash course in colorectal cancer [CRC]. As an informed patient I realised that the treatments that were going to save my life were not necessarily available to me. I knew that in Scandinavia pre-adjuvant treatment was standard for my condition. I knew that total mesorectal excision was the preferred surgical technique. I knew that in North America the standard adjuvant chemotherapy was a combination of 5FU/FA and oxaliplatin. Actually getting these treatments was going to be difficult.

I managed to obtain pre-adjuvant treatment because of a combination of factors. [redacted]. But equally as important was my own knowledge and the persistent and relentless lobbying of my wife and family. My surgeon, [redacted], was instrumental in directing me to my oncologist as the person most likely to be able to facilitate the best treatments. However, I recognise that the only reason that I *did* get pre-adjuvant treatment was

due to serendipity. I just happened to fulfil the entry criteria for a clinical trial that just happened to be recruiting at the time of my diagnosis. Any other time or place and I would have been wasting my breath.

Which is precisely what happened when it came to adjuvant chemotherapy. I did not fulfil any trial criteria. NICE had not approved the treatments that I needed. No amount of supplication, calling in of favours or argument could change this. I had the usual 5FU/FA course.

The effects of my treatment

I appeared to be vulnerable to the side effects of all treatments. In the case of capecitabine I developed hand-foot syndrome, diarrhoea, stomatitis and peripheral neuropathy. Of course it is difficult to eliminate the effects of the other concurrent treatments. I am now free of all these complications.

I did not have oxaliplatin. By way of anecdote, fellow patients that have used this drug report a very similar picture to that described in the literature.

The most important effect of my treatment is that I am alive. Even if I have a recurrence I will have had 9 months [so far] of life, disease free and free of the effects of chemotherapy.

My views

1. Oral versus intravenous administration

The weekly 70 mile round trip to receive my iv bolus of 5FU/FA would take up at least four hours of my time. No clinic can be expected to provide on time appointments given staffing pressures and the variability of clinical need.

It would also take up 4 hours of my wife's time who would have to drive me because of my debilitated state. She is a doctor; the NHS lost 9 months of her work because of my illness. It would take up 4 hours of a carer's time to look after my children whilst I had my treatment. The economic cost to some would be prohibitive. In my case it was a relative, who in turn took time off work from their employment.

The economic implications of oral administration of cytotoxic drugs go beyond the usual measurements. The issues of convenience are not inconsiderable. There will be some patients that will have trouble adhering to a regimen; there will be some patients that miss the support that they receive from staff and fellow patients in clinics. These potential problems can be identified in advance and planned for. What is most important is that we have a choice.

2. The use of oxaliplatin

There are clinical arguments (Joint College Statement) made against the use of oxaliplatin based on its side effect profile. Neurotoxicity is significant risk that may have implications beyond treatment cessation. The manufacturer's claim that only 0.5% of patients had persisting grade 3 problems at 18 months. One could always challenge drug company statistics and this will happen during the course of discussions. However it is less likely that the College's assertions will be challenged and I feel I must do so. It is immensely patronising to both patients and fellow clinicians to pronounce that certain patients [that have more than 3 positive nodes] can have a treatment and others cannot. The implications of such a casual distinction are immense. There is no scientific evidence that will show who will and will not respond and who will and who will go on to develop metastatic disease. It is for patients to decide, not doctors what side effects they are willing to tolerate and what possible complications they are willing to risk. All competent individuals are perfectly capable of saying *no mas* when they have had enough. It should be down to the clinical judgement of individual clinicians to offer appropriate advice about treatments and allow patients to choose their course. To not allow a significant proportion of patients to have this choice is inexcusable.

3. Access to treatments

Most patients do not have access to the information required to make informed judgements. They rely on the clinician to fully appraise them of their options and research findings. It is not possible to dedicate sufficient time to fully satisfy patient's needs, the doctor-patient dynamic and economic considerations can and do limit the information disclosed.

Many patients are so debilitated by their illness, treatments and emotional burden that they fail to assert their wishes. Many patients do not have relatives who are able to act as eloquent advocates. When you are expecting death, it can be difficult to summon the energy required to resist the seemingly inevitable progress of a clinical protocol.

Much of the literature available to patients is out of date, incomplete or sometimes simply misleading. One cannot form opinions on inaccurate data.

I would ask the committee to consider recommending the release of NICE summary and overview documents in a readable form to the public for this appraisal and future appraisals in advance of decision-making. This would give all patients the opportunity to have the same level of information regardless of their professional background, likeability as a person or level of personal contacts. There should be no hierarchy of information in a sound minded NHS.

4. Statistical analysis

The methods used by medical statisticians are based on premises that are inflexible, yet prone to misinterpretation. Evidence based medicine is the *judicious* use of the best available evidence, not the rigid adherence to arbitrary rules.

In this case if one looks at the X-ACT trial, capecitabine had a hazard ratio of 0.87 [C.I. 0.75-1.00]. This result can be interpreted by some to be insignificant because the confidence interval includes 1.00. But to any rational observer it is clear that the most likely hazard ratio is actually 0.87, with an equal chance that it is 0.75 as much as it may be 1.00.

In the same trial the reduced disease recurrence had a significance of 0.0528. This, if one wished to be pedantic, is not statistically relevant. How can it be that when something is shown to occur 95 times out of a hundred rather than 94 it is somehow entirely significant and vice versa?

The point I wish to make is that I would hope that the panel is pragmatic, not dogmatic, in their examination of the statistics. One must recognise that at the end of any statistical process what we are left with is our best guess. A p-value of 0.001 remains a guess. A confidence interval that crosses 1.0 is not insignificant; it is simply awaiting a sample size great enough to satisfy our arbitrary man-made statistical criteria for significance.

Criticisms of the MOSAIC trial may be based on received opinion. I would say that this opinion is at best myopic, at worst negligent. Discounting the findings of the 3 and 4-year survival statistics that clearly show a superior effect of an oxaliplatin 5FU/FA combination because the confidence interval is crossing 1.0 is wrong. The hazard ratio is 0.89 and is very likely to be close to this figure. Not acknowledging that survival to 4 years is important, but rather ignoring it till the 5-year data is in, is wrong. The majority of recurrences occur within 2 years. This injudicious disregard is deeply upsetting to a patient such as myself. When it is as clear as it is that a treatment that may have saved countless lives is being withheld because of statistical dogma, it calls into question the motivations behind the appraisal process.

5. Cost-benefit analysis

This section is perhaps the most difficult for a patient to comment upon. What price do you put on a life? Rather than debate the existing health economy measures I will offer an alternative. An individual patient narrative, my own. The process of calculating compensation for the victims of 9/11 in the USA threw up a welter of scenarios that defied easy tabulation. Each individual is unique, it is futile to attempt to generalise the human condition.

I was in clinic awaiting my first appointment with my oncologist whilst my daughter was being born in another city, in another hospital. Every day of her short life has been under the shadow of my illness. Every day that I have lived subsequently has been lived as time that is probably finite. I have targets that motivate me. To live long enough to teach my boy to ride a bike. To live long enough to have a conversation with my daughter. To live long enough to go to a parents day at school. There is no economic measure, or quantitative assessment that can take these factors in to account. An extra 6 months of life may seem insignificant to healthy individuals, but to people in my position it can mean the difference between a bitter, sad death and an opportunity to do the things that you would want to do before you die.

I am unusual in that I am a lot younger than most of my fellow CRC sufferers. But why should the fact that I do have a "50 year time horizon" make me a more deserving patient than someone who does not? It is a spurious criticism to make that betrays a lack of understanding of human nature. A person's worth is not determined by their age alone. Would those that make such comments withhold treatment from their own parents who might be the 'wrong' side of three score and ten?

Summary

The appraisal process runs the risk of being seen as biased against vulnerable patients, individual choice and patient autonomy. There may be suspicions that use of statistical rigour is a proxy for control over access to efficacious, but expensive treatments. I would urge the panel to have in mind that they are discussing the availability of a drugs that may save hundreds of lives a year and can extend the life of thousands of people a year. It is an imperative that patient's views are taken into account, that patients are given the same information that clinicians have and that patient's are allowed to make the choice about treatments offered. It is a mistake to cite non-maleficence as a reason to withhold drugs. Competent individuals should be allowed to weigh up the evidence and come to their own conclusions. After all no randomised controlled trial, no matter how rigorous or powered it may be, will exactly match the patient sitting in front of you. I hope that the committee will be judicious in their use of the evidence and agree that our best guess at the moment is that both of these treatments are likely to be useful for patients with CRC.

Acknowledgements

I would like to thank my wife [redacted], whose love and dedication has guided me through these terrible days. I owe her my life. I am proud to work for the NHS, an organisation that stood up for me when I needed it.

Dr Anand Sharma, September 2005