PERSONAL STATEMENT

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When I became a consultant in 2002 the sub speciality of renal cell cancer (RCC) was one even the most seasoned of oncologists found daunting. RCC had proved resistant to all known chemotherapy drugs as well as conventional radiotherapy. The only treatment with any proven efficacy was immunotherapy with cytokines whereby the immune system was manipulated to be more effective against the cancer. The standard of care in the UK over the last two decades remains the cytokine interferon-alpha. However, interferon is effective in only 20% of patients at best and improves survival by a modest 2.5 months. Interferon is given as a subcutaneous injection which is unpleasant for patients and is associated with significant toxicities, particularly affecting quality of life, such as fatigue and anorexia. Indeed many patients prove to be intolerant of the therapy and have to stop therapy. Moreover, it is known not to be effective in patients with certain features, such as bony metastases which are very common in RCC, and has many contra-indications, including any history of depressive illness, which further limits its use. For patients who are not eligible for interferon, do not tolerate it or fail interferon therapy there is no second line therapy available in the UK. The only treatment available is palliative care, sometimes known as best supportive care, but in the words of one of my patients it is "care without hope".

The historical perspective is important to reflect the unmet need in the treatment of advanced RCC and to highlight the major advances made within the last 3 years which serves as a paradigm for many of our present and future oncology treatments. Advances in our understanding of cancer biology showed that angiogenesis, the formation of new blood vessels, was a key pathway and a target for new therapies. RCC in particular promised to be particularly sensitive to such treatment and so it has turned out to be with all of the agents under review targeting some aspect of the angiogenesis pathway. The first two new agents to be licensed in the EU were sunitinib and sorafenib, both in July 2006, for both first and second line therapy. In the absence of NICE guidance the decision to fund new drugs is left to the individual primary care trusts (PCTs). All the evidence is that the majority of PCTs are not widely funding these drugs but that there exists the so called post code lottery. In addition, the availability of these new drugs through private health insurance is giving rise to a two-tier health care system in the treatment of RCC.

The major experience of these new drugs in the UK to date is with sunitinib with the largest expanded access program running in the UK in 2006. Both sorafenib and temsirolimus have also had expanded access programs of more limited nature and I have no personal experience of either of these drugs in this setting. Bevucizumab did not have an expanded access program although I did recruit a few patients into the AVOREN trial. We entered 27 patients into the sunitinib expanded access program at the [redacted] between April and August 2006. The first impression was of good tolerability with only one patient stopping treatment and two hospital admissions due to direct toxicity. The major toxicities seen were fatigue, stomatitis and hand-foot syndrome, very much as expected from the clinical trial data. The

latter two toxicities were different to that seen with traditional chemotherapy in that the presenting symptom was pain before any physical lesions were seen. However, these toxicities were manageable by prompt dose reduction and in our experience 50% of our patients required dose reduction from 50mg to 37.5mg. The subjective impression was that quality of life was very good on sunitinib. The second impression was of excellent efficacy compared historically with our experience of interferon. At 6 months 50% of patients were still on treatment with stable disease or better. Furthermore we did see responses with bony metastases with sunitinib which we would not expect to see with interferon. The third impression was that the oral nature of sunitinib was clearly preferable to interferon for patients. Furthermore, from a hospital resources perspective, oral drugs such as sunitinib and sorafenib imposed no additional pressure on the chemotherapy units unlike an intravenous new drug.

Currently there are three randomised first line clinical trials against interferon-alpha as the standard therapy, with the comparator arm using sunitinb, bevacizumab + interferon combination or temsirolimus. I will consider sunitinib and bevacizumab + interferon together as both trials had similar entry criteria and focused on fitter patients. Both trials give very similar efficacy data with median progression free survivals of 11 months for sunitinib versus 5 months for interferon alone and 10.2 months for bevacizumab + interferon versus 5.4 months for interferon alone. Overall survival figures are not available yet for these studies. The bevacizumab study looked at prognostic factors as well and patients with poor prognostic factors did not benefit from the addition of bevacizumab to interferon, which may allow for targeting of bevucizumab + interferon to a subgroup with more favourable prognostic factors. For sunitinib there appeared to be benefit across the prognostic groups although numbers in the poor prognosis group were small. The doubling in progression free survival time is statistically significant but it must also be appreciated that in a wider context doubling of progression free survival by any new therapy is rare in oncology and all the more remarkable.

The temsirolimus study was designed differently to the above two studies in that it was a three arm design comparing temsirolimus versus temsirolimus + interferon versus interferon in patients with poor prognostic factors. This is the only trial to give an overall survival benefit of 10.9 months for temsirolimus versus 7.3 months for interferon. The difficulty of this study is that the patient group selected overlaps with the patient groups treated in the sunitinib and bevacizumab trials but it is not possible to directly compare the agents because the prognostic factors were different for the studies.

There is only one randomised clinical trial in a second line setting and that is for sorafenib versus placebo after first line cytokine failure. The TARGETs study showed that sorafenib improved progression free survival from 12 weeks with placebo to 24 weeks with sorafenib. Overall survival benefit is impossible to define given that the FDA terminated the trial early and mandated that all surviving patients be crossed over to sorafenib. There are currently no published randomised clinical trials in a second line setting after failure of sunitinib, sorafenib, bevacizumab or temsirolimus. However, there are many anecdotal reports as well as impending clinical trial data to suggest that these agents do have sequential activity.

The issue of overall survival deserves a short comment. This remains one of the gold standards for any cancer treatment. However, as the TARGETs study demonstrated premature termination of the study and cross over will confound this end point.

Furthermore, as more drugs become licensed for the treatment of RCC there is ample evidence that in many countries patients progressing on one drug will be simply switched to another drug regardless of the lack of any randomised clinical trial evidence. If this happens in a clinical trial setting then again this will confound any overall survival benefit. There remains much debate about progression free survival as a surrogate measure but clearly in the case of RCC there are compelling reasons to accept this as a valid end point in assessing efficacy and benefit.

I believe that there are three imperatives for NICE in assessing these new agents for the treatment of advanced RCC. First and foremost, interferon as the current first line standard of care should and must be replaced by sunitinib and/or bevucizumab + interferon in fit patients. The choice between these two agents may be determined by health economics, but health economics should not be used to reject these treatments. It must be recognised that these treatments fill an unmet clinical need, and that the NCRI renal cell cancer subgroup of specialists have issued a statement declaring that such drugs should be the new standard of care in line with similar recommendations in Europe and North America. The role of temsirolimus would seem to be more restricted to those patients with poor prognostic factors and the clinical trial is the only one with an overall survival benefit.

The second imperative would be to approve sorafenib for second line treatment in patients who have failed cytokine therapy. As interferon remains the only approved treatment in the UK currently there will be significant number of patients with advanced RCC who will have already been exposed to this cytokine and no other therapy. Sorafenib has the only randomised evidence in this setting.

The third imperative for NICE is to meet the challenge of rapid developments in this field. The introduction of at least four new therapies for any tumour type within 2 years is unprecedented but has also left many unanswered questions regarding their optimal use. The most pressing studies include head to head comparisons to determine which agents are best and sequential studies to optimise the order of treatment with these new drugs. Such studies have been conducted or are being carried out and the results will be published over the course of the next few months to years with important clinical consequences. This will call for regular and frequent review by NICE to keep the guidelines updated and clinically relevant.

In 2002 looking after patients with advanced RCC was depressing but at least there was an honest understanding between doctor and patient that there was only one treatment available which was not particularly effective yet was toxic. In 2008 we have a situation where clinicians, patients and their carers know that there are more effective and better tolerated treatments licensed and yet their availability is determined by post code lottery. It seems that much more cruel when “care without hope” is because of human decision rather than lack of knowledge. The single most important imperative for NICE must be to change this.