

NCRI Renal Cancer Clinical Studies Group

Introduction

Renal cancer is uncommon but there are still over 6000 new cases per year and the incidence appears to be rising. Renal cancer is notoriously unresponsive to chemotherapy and radiotherapy and this has led to the investigation of new agents targeting molecular pathways. The last 5 years has seen considerable interest in renal cancer from the pharmaceutical industry with several new agents being developed which have shown significant increases in progression-free survival and overall survival. None of these agents are curative and all are expensive and although several have received a licence and have become standard of care worldwide, it is only in March of this year that NICE has approved the use of a single agent in first-line metastatic renal cancer. This has meant that the United Kingdom has significantly lagged behind other Countries as they have not had a funded standard of care to offer in first-line or second- line trials in metastatic disease.

Membership and structure

Membership has been expanded to include more representation from Urology and Clinical Oncology. Mr Rupesh Bhatt, Mr Damian Hanbury, Dr Angela Meade, Dr Philip Savage and Mr Naeem Soomro have all joined the Group whilst Professors Barry Hancock, Poulam Patel, and Hardev Pandha, Ms Helen Parrott, Dr Amit Bahl and Mr Alistair Ritchie have all left the Group. There is expert pathological representation and several of the members have major translational research interest.

It had been previously felt that to develop a sub-group structure in the relatively uncommon tumour was probably not profitable but an experimental ad hoc new drug development group was instigated and this has proved to be very fruitful. This has been extended to a Surgical Subgroup looking specifically at treatment of small renal tumours.

Portfolio and accrual

The current list of trials in the portfolio can be found in Table 1 below.

Accrual into renal cancer trials has increased from 2.9% of incidence cases in 2007-8 to 5.1% in 2008-9, an increase from 169 to 296 patients. 3.85% of incidence cases were recruited to RCTs and 1.25% to non RCTs.

Table 1: Renal Cancer CSG portfolio

Acronym	Title	PI(s)	Status
HYDRA	Adjuvant interleukin-2, interferon-alpha and 5-Fluorouracil for patients with high risk of relapse after surgical treatment for renal cell carcinoma	Mr Michael Aitchison	Closed
IL2 +/- SRL 172	A phase II randomised prospective study comparing Interleukin-2 versus	Professor Peter Selby	Closed

	Interleukin-2 with SRL 172 in patients with advanced renal cell carcinoma		
NCRN008	NCRN008 - Industry study	Dr Matthew Cooper	Closed
NCRN044 - INDUSTRY STUDY	A study of Pazopanib versus Sunitinib in the treatment of subjects with locally advanced and / or metastatic renal cell carcinoma	Dr Matthew Cooper	Closed
NCRN055	Axitinib (AG-013736) as second line therapy for metastatic renal cell cancer : AXIS TRIAL	Ms Lucinda Gray	Open
REO4	A randomised trial of interferon-alpha, interleukin and Fluorouracil versus interferon-alpha alone in advanced renal cell cancer	Professor Martin Gore	Closed
SORCE	A phase III randomised controlled study comparing Sorafenib with placebo in patients with resected primary renal cell carcinoma at high or intermediate risk of relapse	Professor Tim Eisen	Open
TRANSORCE (sub-study of SORCE) -	A study to collect blood and tissue samples from consenting patients who have been diagnosed with renal cell cancer.	Professor Tim Eisen	Open

Two major trials have recently closed, the HYDRA adjuvant trial and the REO4 randomised trial of triple regime of interleukin-2, 5-Fluorouracil and interferon-alpha versus interferon-alpha alone in advanced renal cancer. This trial represents the largest clinical trial ever performed in metastatic renal cancer and the results of this and the HYDRA trial were both presented at ASCO in 2008. A submission to The Lancet of the REO4 results has been made and is currently being considered by that journal. The HYDRA trial presented only interim results at ASCO 2008 and the complete results will be available to March 2010 and a submission is planned to ECCO in 2010.

The infrastructure and participating groups built up in the REO4 and HYDRA trials were used to launch the SORCE trial. This trial is recruiting on target and has a major translational component.

Trials in development

As mentioned in the introduction, the UK has been at a significant disadvantage compared with the rest of the developed world as it has not had a standard of care in the form of a target agent for first-line metastatic disease until the NICE decision in March this year.

The members of the Renal CSG have been active in planning new trials. A proposal had been submitted to CTAAC which arose out of the AstraZeneca collaboration which will examine a new agent and second-line treatment in combination with a novel compound which will target a separate pathway in the renal tumour cells.

Two further proposals have been discussed in first-line patients. The first is an intermittent versus continuous Sunitinib protocol looking at ameliorating the toxicity but maintaining the efficacy of this agent and it is hoped to submit this to the next CTAAC meeting. A further trial has been discussed looking at Interferon/sunitinib cross-over in good performance status patients and a draft protocol will be circulated to members of the CSG shortly.

A study proposal for non-clear cell tumours has been developed by colleagues in Duke in the USA and discussions have led to an agreement for 6 UK centres to participate and the protocol will be submitted to the next CTAAC meeting.

Four surgical studies are being considered. The first study, CARMENA, in conjunction with the French Renal Cancer Group is a trial of nephrectomy followed by Sunitinib treatment versus no nephrectomy and Sunitinib treatment alone in patients presenting with metastatic renal cancer. This is a repeat of the pivotal EORTC/SWOG study which demonstrated a survival benefit for cytoreductive nephrectomy. The second trial is in conjunction with the EORTC GU Group and will examine the timing of Sunitinib treatment comparing neo-adjuvant with adjuvant Sunitinib in patients who will all receive nephrectomy. The CSG feel that these studies will be complimentary in a trial portfolio rather than competing giving the dichotomy of view that patients often have regarding nephrectomy. Submission to the next CTAAC Meeting is planned for both studies. Two further surgical studies are being developed, one looking at minimally invasive treatment such as RFA and cryoablation versus partial nephrectomy. The Health Technology Appraisal Funding Group would seem most appropriate for this trial and this is being pursued. The second surgical trial is of observation of small renal masses in elderly or frail patients and the NIHR Research for Patient Benefit funding stream.

Meetings

The Renal CSG alongside the other three Urological CSGs held a National Urological Cancer Trials meeting in January 2009. This attracted a large attendance of oncologists, urologists, research nurses and other allied professionals and showcased the trial activity in urological oncology and provided an extremely good forum for discussion of potential new trials.

Collaborations

Collaborations with the EORTC Urological Group and the French CARMENA Group have been detailed above. In addition to this SORCE is a multinational trial and an Australian Group (APUG) have become participants in the trial and are keen to collaborate on further projects. The non-clear cell trial proposal mentioned above involves investigators from the United States and discussions have also been held with the Canadian Renal Cancer Group headed by Professor Michael Jewett about possible participation in the small renal tumour studies mentioned previously.

Other activities

In view of the low percentage of patients entered into clinical trials in the UK for renal cancer, the NCRI Clinical Studies Group used a project officer funding grant to commission a report into renal trial accrual and the problems surrounding this and this is attached as Appendix 2. It is clear from the average yearly accrual shown in this report that it is possible to achieve almost 10% accrual from some centres and the comments and future portfolio priorities identified by the participants have been discussed fully by the Renal CSG.

3-year strategy/priorities for next year

The new Chair has recognised the urgent need to increase the number of trials in the Renal CSG portfolio. There is currently only one open trial in the adjuvant setting. A pragmatic approach will be required and the adoption of industry trials will clearly be necessary to broaden the Renal CSG portfolio but the submission of an investigator-led trial in second-line treatment for metastatic disease to CTAAC in the current funding round has been a major achievement and there is clearly a need to follow this with further funding submissions and also to broaden the range of funding bodies approached.

Mr Michael Aitchison, Chair

Appendix 1

2008/09 Publications and abstracts

PM Patel, S Sim, DO O'Donnell, A Protheroe, D Beirne, A Stanley, JM Tourani, K Khayat, B Hancock, P Vasey, A Dalgleish, C Johnston, RE Banks, PJ Selby. An evaluation of a preparation of *Mycobacterium vaccae* (SRL172) as an immunotherapeutic agent in renal cancer. *Eur J Cancer* 44:216-223,2008.

BW Hancock, P Nathan, A Richie, R Hawkins, J Wagstaff, J Anderson, ND James, P Patel, T Eisen, D Chao, M Gore. Effective new treatment for patients with advanced renal cell carcinoma. *BMJ letter* 11th September 2007.

M. Aitchison, C. Bray, H. Van Poppel, R. Sylvester, J. Graham, C. Innes, L. McMahon, P. A. Vasey Preliminary results from a randomized phase III trial of adjuvant interleukin-2, interferon alpha and 5-fluorouracil in patients with a high risk of relapse after nephrectomy for renal cell carcinoma (RCC). *J Clin Oncol* 26: 2008 (May 20 suppl; abstr 5040)

M.E.Gore on behalf of all RE04 Investigators. Interferon- α (IFN), Interleukin-2 (IL2) and 5-Fluorouracil (5FU) vs IFN alone in patients with metastatic renal cell carcinoma (mRCC): Results of the randomised MRC/EORTC RE04 trial. *Journal of Clinical Oncology, 2008 ASCO Annual Meeting Proceedings, 26, abstract 5039.*

Ramsey S, Lamb GW, Aitchison M Prospective study of the relationship between the systemic inflammatory response, prognostic scoring systems and relapse-free and cancer-specific survival in patients undergoing potentially curative resection for renal cancer. *BJU International* 2008 Apr; 101 (8): 959-63

Ramsey S, Ganai B, McMillan DC, Graham JD, Aitchison M Use of an inflammation-based prognostic score in patients with metastatic renal cancer treated with Sorafenib. European Urology Association Annual Meeting Berlin 2007 Abstract 963 *Eur Urol Suppl* 2007; 6 (2): 263

Nathan P, Wagstaff J, Porfiri E, Powles T, Eisen T UK guidelines for the systemic treatment of renal cell carcinoma *British Journal of Hospital Medicine* ,2009,70(5),284-286