Improving the impact of clinical research: A systematic analysis of kidney cancer trials

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Background

ClinicalTrials.gov is one of the largest databases of clinical research in the world, comprising over 120,000 trials in 175 countries. With over 50 million page views a month, it is also the most utilized source for clinical trial information worldwide. As of 2007, registration was mandated for clinical trials expected to contribute to an FDA submission. In addition, the International Committee of Medical Journal Editors mandated inclusion of trials in a public registry at the time of enrollment initiation in order to later consider them for publication in peer-reviewed medical journals.

This project analyzes the portfolio of trials available on ClinicalTrials.gov through a collaboration between the FDA and Duke University, as part of the Clinical Trials Transformation Initiative (CTTI). In particular, we analyzed the renal cell carcinoma (RCC) trial portfolio. RCC is an area of great change over the past few years, with new treatments available and uncertainty as to the role and evidence base for different agents. Can an improved understanding of the research portfolio move the field forward?

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Methods

- A dataset comprising 96,346 clinical trials was downloaded from ClinicalTrials.gov on September 27, 2010 in XML format and a database for the Aggregate Analysis of ClinicalTrials.gov (AACT) was created to facilitate analysis.
- A subset of trials was identified, corresponding to the FDA enactment of mandatory registration in 2007.
- A process was developed to annotate and validate disease conditions in order to create specialty datasets. A combination of National Library of Medicine (NLM) MeSH terms and additional non-MeSH (free-text) terms were annotated by disease, resulting in a summary algorithm used to classify trials as depicted in Figure 1.
- Trials identified as "oncology" were then manually reviewed by clinicians to exclude false-positive studies and further classify the oncology trials by cancer type.
- The characteristics of trials identified as RCC-specific were further analyzed.
  - Those registered after October 2007 were excluded if trial start dates predated registration or the trial did not assess treatment agents.
  - Trial attributes were verified using entries on ClinicalTrials.gov as of January 2012.
  - The treatment agents in trials were categorized as: included in NCCN guidelines, FDA-approved but not included in NCCN guidelines, or novel (not FDA approved).

Results

- Of 40,970 interventional studies registered between October 2007 and September 2010, 8942 (22%) focused on oncology, the highest among all specialties represented.
- 108 RCC trials studied treatment agent(s) which were registered and initiated in the defined timeframe.
- 48% assessed agents included in the NCCN RCC Guidelines at the time of study initiation and 18% studied FDA-approved treatments that were not included in the guidelines. 34% of trials included a novel agent.
- As shown in Table 1, less than third of trials were randomized, blinded, multi-arm, or late-phase (Phase III or IV), regardless of the approval status of the study agent. 60% of studies are industry sponsored and <1% included overall survival as a primary endpoint.
- Across all RCC trials from 2007-2010, 50% are listed as recruiting, 24% open but not recruiting, 10% unknown, 8% withdrawn/terminated, and 8% complete. Of the 46 trials started between 10/2007 and12/2008, 39% are open but not recruiting, 24% recruiting, 13% withdrawn/terminated, 13% unknown, and 11% complete.

Limitations

- There are limits to the registry's comprehensiveness as there is no obligation to register phase I trials that do not involve a device or drug or to register trials conducted solely outside US jurisdiction.
- Missing data, the medical sophistication of persons entering the data, ambiguous terminology, and free-text input options all further complicate analysis efforts.

Conclusions

- The ClinicalTrials.gov database provides a unique opportunity to understand the breadth of interventional trials in oncology.
- Optimizing clinical research includes increasing studies of novel therapeutics and improving the comparative effectiveness research portfolio by increasing utilization of pragmatic designs, registries and late-phase trials.
- The findings identify strengths and weaknesses in trial design, patient populations, and evidence development that need to be carefully considered in an era of increasing focus on research design and comparative effectiveness research.
- The majority of new studies and accrual in RCC assess questions of treatment sequence and setting for established therapies, many of which lack rigorous design. These insights need to be incorporated into funding decisions and similar analyses are needed for other cancer types.

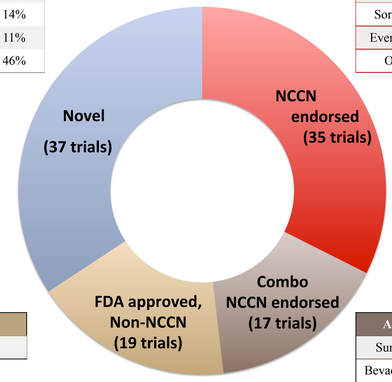
Table 1. Attributes of clinical trials in renal cell cancer by approval status of study agent(s), 2007-2010.

Characteristics		All agent(s) included in NCCN-guidelines (n=52)	FDA-approved agent(s) not in guidelines (n=19)	Non FDA-approved agent(s) (n=37)
Total Trials		48%	18%	34%
Trial Design				
	Randomized	33%	16%	24%
	Blinded	6%	0%	8%
	Multi-arm	33%	16%	32%
	Phase III/IV	13%	5%	11%
Sponsor and/or collaborator				
	Industry	50%	58%	76%
	Government	15%	32%	14%
	Other	77%	58%	35%
Overall survival endpoint				
	Primary	2%	0%	8%
	Secondary	56%	47%	24%
	Not included	42%	53%	68%

Figure 1. Grouping Trials into Specialty Datasets (adapted with permission by Tasneem, ACRT 2011)

Figure 2. Stage of development of study agent across renal cell carcinoma trials, 2007-2010.

Agent	% trials
TKI	38%
Vaccine	14%
HDAC	11%
Other	46%



Agent	% trials
Sunitinib	51%
Sorafenib	20%
Everolimus	20%
Other	9%

Agent
Various

Agent	% trials
Sunitinib	59%
Bevacizumab	41%
Temsirolimus	24%
Everolimus	24%

TKI – tyrosine kinase inhibitor, HDAC – histone deacetylase