Clinical research and care in the era of ‘N-of-1’ precision cancer medicine

Prof. Maurie Markman – Cancer Treatment Centers of America, USA

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Cancer Treatment Centers of America
Clinical Professor of Medicine
Drexel University College of Medicine

Randomized trials in cancer medicine

- Well-established paradigm which has helped to establish the ‘standard-of-care’ in the treatment of malignant disease
- Including both efficacy/toxicity of surgery, radiation, anti-neoplastic drug therapy (cytotoxic, ‘targeted’, immunotherapeutic agents) and multi-modality approaches to cancer management
- Importantly, helped end practices based on ‘physician belief/experience’ rather than objective clinical evidence (e.g., radical mastectomy in early stage breast cancer)

Randomized trials in cancer medicine

- In the arena of anti-neoplastic drug therapy randomized trials have helped define doses, schedules, durations, as well as short-term and long-term side effects
- *Placebo or no-treatment controls have helped to define the survival and symptom-duration/severity impact of therapy (positive or negative) compared to the natural history of the disease process*

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So, what is wrong with this picture?

- Increased recognition that the fundamental goal of the randomized trial, to insure homogeneity of the population to ‘isolate’ the impact of the strategy in question may seriously undermine the ultimate clinical utility of the trial outcome in the ‘real world’ of cancer care
  - Age; Co-morbidities; Extent prior treatment, metastatic spread; Relevant ‘sub-groups’

So, what is wrong with this picture?

Are the patients who were treated on this trial are the same as my patients?
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So, what is wrong with this picture?

- Increasing time, effort, and costs associated with the completion of randomized trials
- Increasing availability of highly reasonable strategies/drugs outside the confines of randomized trials (So, why should a patient participate in this study?)
- Increasing availability of approaches with documented clinical utility following trial completion that may realistically impact the clinical outcome (particularly relevant where overall survival is the primary endpoint)

Problems with overall survival as the only acceptable study endpoint

Detecting an Overall Survival Benefit that Is Derived From Progression-Free Survival

Kristina R. Bright, Donald A. Bens


Hypothetical trial

280 patients with a 3-month median improvement in progression-free survival

# of patients necessary to reveal improved overall survival based on median post-trial survival:

<table>
<thead>
<tr>
<th></th>
<th>2 months</th>
<th>24 months</th>
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<tbody>
<tr>
<td>2 patients</td>
<td>350 patients</td>
<td></td>
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<tr>
<td>2,400 patients</td>
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</table>

Problems with overall survival as the only acceptable study endpoint

Median survival following 2 second-line carboplatin/gemcitabine chemotherapy ‘study arms’ in potentially platinum-sensitive recurrent ovarian cancer

<table>
<thead>
<tr>
<th></th>
<th>PFS</th>
<th>Overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial initiated 1999</td>
<td>8.6 months</td>
<td>18.0 months</td>
</tr>
<tr>
<td>Trial initiated 2007</td>
<td>8.4 months</td>
<td>35.2 months</td>
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Problems with overall survival as the only acceptable study endpoint

Surrogate endpoints for overall survival in metastatic melanoma: a meta-analysis of randomised controlled trials
Keith T Flaherty, MD.
• Early precision medicine-based trials versus “controls”
• Relationship between PFS and OS: (correlation coefficient) 0.96

More recent experience:
Relationship between PFS and OS: (correlation coefficient) 0.55

Other issues with existing cancer clinical trials paradigm

• Difficulty for individual patient to access a clinical trial (limited study locations; uncertain “insurance coverage”; major time commitment for the patient/family)
• End result, currently <4% of cancer patients in the United States participate in a clinical trial and the percentage of patient participation in randomized trials will be considerably less

Ongoing/accelerating paradigm-change in cancer management

• Revolution in our understanding of the molecular biology of cancer and specifically drivers of growth, spread, resistance in individual cancers
• What was once solely “organ-based” cancer treatment (breast, colon, lung) has rapidly evolved to (organ + molecular target-based) treatment
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Ongoing/accelerating paradigm-change in cancer management

Breast:
ER/PR+/-, Her2 +/-
Lung:
EGFR mutation;
Alk-rearrangement
Melanoma:
BRAF mutation +/-

Impact on cancer trials

• 20-25% of breast cancer (HER2+) or non-small cell lung cancer (EGFR mutation+) or 50% of metastatic melanoma (BRAF mutation+) would be considered a reasonably large population to conduct a phase 3 trial
• But what about 1% of lung cancers (ROS1 rearrangement) or < 10% of the population of a far less common/rare tumor type (ovarian cancer)?

Impact on clinical trials

• And even if able to conduct a randomized trial in a rarer cancer when this is only access to a novel agent (BRCA mutation+ ovarian cancer), what happens to the next generation of trials when an effective treatment (PARP inhibitor) becomes clinically available?
• Why would patients enter such randomized trials versus seeking the best possible available treatment for their condition?
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The future of individual non-research somatic molecular testing

- It is now possible to sequence the entire genome of a tumor (and corresponding germline) of an individual cancer patient for less than US $5,000 ($20 years ago this would have cost considerably more than US $1,000,000,000)
- Multiple "NGS platforms" being investigated and currently available, including increasingly expanding so-called "actionable" gene panels (ranging from 50-500+ genes)

Proposed theoretical alternatives to randomized trials

- Population-based studies of surgery, radiation, anti-neoplastic drug therapy (commercially available agents delivered ‘on’ or ‘off’-label) examining survival, toxicities, hospitalization
- Registry (‘public’ or ‘for-profit’) databases established specifically for the purpose of evaluating the utility of ‘targeted’ therapeutics (ASCO’s CancerLinQ)
- Individual institutional peer-reviewed publications of ‘case reports’ or ‘case series’
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Example: population-based study

Aspirin Use, Tumor PIK3CA Mutation, and Colorectal-Cancer Survival

Xiaoyun Liao, M.D., Ph.D., Paul Lochhead, M.B., Ch.B., Reiko Nishihara, Ph.D., Teppi Monkawa, M.D., Ph.D., Aya Kuchiba, Ph.D., M. Yamauchi, Ph.D., Yu Imamura, M.D., Ph.D., Zhi Rong Qian, M.D., Ph.D., Yoshifumi Baba, M.D., Ph.D., Kaori Shima, D.D.S., Ph.D., Rui Cai, M.D., Ph.D., Katsuhiko Nosho, M.D., Ph.D., Jeffrey A. Meyerhardt, M.D., M.P.H., Edward Giovannucci, M.D., M.P.H., Sc.D., Charles S. Fuchs, M.D., M.P.H., Andrew T. Chan, M.D., M.P.H., and Shuji Ogino, M.D., Ph.D.

Example: population-based study

• Aspirin use and survival after colon cancer diagnosis
• Two populations detailed health information:

- 121,000 Nurses Health Study 1976
- 51,000 Health Professionals Follow-up Study 1986

964 developed colon cancer; tumor examined
17% patients PIK3CA mutation

Example: population-based study

• Aspirin use and survival after colon cancer diagnosis
• Presence of PIK3CA mutation in the tumor:
  82% reduction in risk of death if took aspirin compared to patients who did not take aspirin
• No impact for aspirin if wildtype PIK3CA
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‘N-of-1’ research paradigm

- Retrospective review and collection of experiences of
- The prospective collection of multiple individual experiences involving the use of a specific anti-neoplastic agent directed against a potentially “actionable” molecular biomarker proposed to be a biologically and clinically relevant (“driver”) target.

Examples of questionable conclusions drawn from current trials paradigm

- Phase 2 randomized trial comparing drug selection based on a proposed molecular “target” vs. drugs not selected based on “targeting”
- No difference in clinical outcome between study arms
- PROBLEM: minimal/no evidence the drugs employed in the study were biologically/clinically relevant in favorably impacting the proposed molecular target

Molecularly targeted therapy based on tumour molecular profiling versus conventional therapy for advanced cancer (SHIVA): a multicentre, open-label, proof-of-concept, randomised, controlled phase 2 trial

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"EGFR is not a relevant molecular target" in ovarian cancer

EGFR "overexpression" is not clinically relevant


"EGFR is not a relevant molecular target" in ovarian cancer

Phase II Study of Gefitinib in Patients with Relapsed or Persistent Ovarian or Primary Peritoneal Carcinomas and Evaluation of Epidermal Growth Factor Receptor Mutations and Immunohistochemical Expression: A Gynecologic Oncology Group Study


27 evaluable patients
4% response rate
9% of patients with EGFR+ tumors

1 responding patient, tumor possessed a mutation in catalytic domain EGFR

Only 3.5% of ovarian cancers (2 of 57) analyzed had such mutations

"EGFR is not a relevant molecular target" in ovarian cancer

But, what about the presence of an EGFR "mutation"?

1 responding patient, tumor possessed a mutation in catalytic domain EGFR

Only 3.5% of ovarian cancers (2 of 57) analyzed had such mutations

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**HER-2 overexpression is not clinically relevant in ovarian cancer**

- Previously treated ovarian cancer
- Eligible: 2+ or 3+ HER2 overexpression by immunohistochemistry
- 837 cancers screened;
- 95 cancers (11.4%) 2+ or 3+
- 54 patients treated
  - (41 assessable – 14 tumors 3+)
  - 7.3% response rate
    - (1 CR; 2 PRs)

? ‘Negative trial’?

Evaluation of Monoclonal Humanized Anti-HER2 Antibody, Trastuzumab, in Patients With Recurrent or Refractory Ovarian or Primary Peritoneal Carcinoma With Overexpression of HER2: A Phase II Trial of the Gynecologic Oncology Group
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Evidence that “molecular matching” favorably impacts clinical outcomes

Pilot Study Using Molecular Profiling of Patients’ Tumors to Find Potential Targets and Select Treatments for Their Refractory Cancers


86 patients with refractory metastatic cancers
- 98% molecular target discovered
66 patients treated according to molecular profiling results
18 patients (77%) had a PFS ratio ≥ 1.3 compared to their most recent prior ratio

Evidence that “molecular matching” favorably impacts clinical outcomes

Personalized Medicine in a Phase I Clinical Trials Program:
The MD Anderson Cancer Center Initiative

Apostolis-Alexander, Nancy G. Seidman, David S. Hong, Jennifer J. Wheler,
Gerald S. Flickinger, Siping Fu, Sameh Fatah, Aung Htay, Filip Janku, Rajapaksarani
Luthria, Yang Yue, Sijin Yue, Donald Berry, Rasaia Kurzrock

460 (40.2%) of 1,144 patients had ≥ 1 molecular abnormalities

Evidence that “molecular matching” favorably impacts clinical outcomes

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Response rate

Time to RX failure (median)

Overall survival

Matched therapy (n=173)

27%

5.2 months

13.4 months

No match (n=116)

5%

2.2 months

9 months

(p<0.001)

(p<0.001)

(p<0.017)

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22 Evidence that “molecular matching” favorably impacts clinical outcomes

Prospective study comparing outcomes in patients with advanced malignancies on molecular alteration-matched versus non-matched therapy.

339 (68%) of 550 patients signed consent were tested, 95% ≥ 1 molecular alterations (Foundation Medicine NGS platform)

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<tr>
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<th>PFS (median)</th>
<th>OS (median)</th>
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<tr>
<td>Matched patients</td>
<td>3.9 months</td>
<td>10.8 months</td>
</tr>
<tr>
<td>(n=110)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unmatched patients</td>
<td>3.3 months</td>
<td>7.5 months</td>
</tr>
<tr>
<td>(n=49)</td>
<td>(p&lt;0.002)</td>
<td>(p=0.018)</td>
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23 Phase 2 “Basket trials”

- **TAPUR** (Targeted Agent and Profiling Utilization Registry) Study
- Sponsor: ASCO
- Non-randomized phase 2 trial commercially available molecularly-targeted agents
- Currently: 7 pharma sponsors; 15+ drugs
- Trial treatment based on discovering a relevant “actionable target” in the patient’s cancer that may be favorably impacted by the “off-label” administration of an anti-neoplastic (among the included drugs)

24 Conclusion

- In the current era it is essential that novel trial designs (e.g., “basket trials”; “N-of-1” response rates with individual PFS durations serving as an internal “control”, etc.) be developed to accelerate the rate of introduction of effective anti-neoplastics into routine clinical practice
- In addition, innovative strategies are required to be developed to help evaluate the efficacy, toxicity, and cost-effectiveness of new approaches in the “real-world” population of cancer patients