The changing nature of cancer clinical trial design

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Birmingham, February 5th 2020
Agenda

- My personal journey – messages from some ‘oldies but goodies’!
  - Measuring quality of life as an important outcome measure
  - Benefits of simple data collection
- Overview of clinical trial pathway for drug development and how it has changed
  - Phase I – involving statistical modelling for more accurate dose-finding
  - Phase II – introduction of randomised designs allowing more relevant outcome measures
  - Phase III – adaptive designs to allow multiple arms, multiple stages and platform trials
- Changes in trial designs to move towards stratified/personalised medicine
  - Initial changes to explore predictive biomarkers using correlative studies within trials
  - How better understanding biology dramatically changed trial design: investigating targeted treatments in molecularly-defined cohorts – umbrella and baskets
- Questions

Thanks to Karen Turner, Cancer Research UK Senior Nurse, CRCTU, Birmingham
The Start of My Personal Journey in 1994

Mitomycin, Ifosfamide, and Cisplatin in Unresectable Non-Small-Cell Lung Cancer: Effects on Survival and Quality of Life


- Single arm phase II N=66
  - 43 localised disease (LD)
  - 23 extensive disease (ED)

Objective response rate:
  - 67% in LD
  - 35% in ED

Unresectable NSCLC

Localised disease
MIC1 Trial

MIC + RT
RT

Advanced disease
MIC2 Trial

MIC + PC
PC

Overall survival time
Quality of life
Example: ‘Simple’ Phase III Trial That Changed Clinical Practice But Only Marginally Improved Outcome

Median survival times:
- MIC1 CT+RT: 11.7
- MIC1 RT: 9.7
- MIC2 CT+PC: 6.7
- MIC2 PC: 4.8
BTOG2 Trial: Comparison of Chemotherapy for Advanced Non-Small Cell Lung Cancer (Ferry, Billingham, Jarrett, O’Byrne; 2005-2009)

Primary Outcome Measure: survival time
BUT QoL assessed in ALL patients for FULL survival time
### Measuring Quality of Life in BTOG2 Trial

<table>
<thead>
<tr>
<th>Patient-completed Questionnaires</th>
<th>Number of QoL Measures</th>
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<tbody>
<tr>
<td>EORTC QLQ-C30</td>
<td>15</td>
</tr>
<tr>
<td>EORTC LC13</td>
<td>10</td>
</tr>
<tr>
<td>EQ5D</td>
<td>2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>27</strong></td>
</tr>
</tbody>
</table>

#### Weeks

- **0** Baseline
- **3** Pre-Cycle 2
- **6** Pre-Cycle 3
- **9** Pre-Cycle 4
- **12** End of treatment
- **16** Follow-up Visit 1
- **20** Follow-up Visit 2
- **24** Follow-up Visit 3

- **Type of measure:**
  - (a) 3 general (1 utility)
  - (b) 5 functional
  - (c) 19 symptom
- **Scores 0 to 100:**
  - (a)&(b) Poor to Good
  - (c) Good to Poor
- **10 point difference in means pre-specified as clinically relevant**

- N=1363; 97% participated
- > 8000 questionnaires returned
- Number returned per patient: median = 6; maximum = 35
- 92% compliance at baseline
- 89% compliance during treatment

Largest reported study of quality of life in lung cancer
Carboplatin versus two doses of cisplatin in combination with gemcitabine in the treatment of advanced non-small-cell lung cancer: Results from a British Thoracic Oncology Group randomised phase III trial

Median survival time

- GC80: 9.5
- GC50: 8.2
- GCb6: 10.0

Log-rank test for difference, unadjusted: p=0.046

Cox model test for difference, adjusted for stage and performance status: p=0.01
Simple
Investigation in Neutropenic Individuals of the Frequency of Infection after Chemotherapy +/- Antibiotic in a Number of Tumours

Solid tumours or lymphoma
Receiving multi-cycle chemotherapy
At risk of short-term severe neutropenia and infection

RANDOMISE

Levofloxacin
Placebo

once daily 7 days to cover anticipated nadir

Primary outcome measure: Incidence of clinically documented febrile episode attributed to infection

Michael Cullen
Neil Steven
Lucinda Billingham
Mark Hastings
Claire Gaunt
### The Significant Trial: On/Off-Study Form

**Prescription details:**
- Patient name ...........................................
- Patient trial number ..................
- Treatment pack number ...............  
- Starting day in cycle ..............

**ON-STUDY SECTION**
Please complete for all cycles of chemotherapy given (up to 6), whether or not trial medication given.

**PART A:** Please complete on the day that you prescribe the chemotherapy and trial medication.

1. Date when chemotherapy cycle will start .......................  
2. Date when trial medication will start .......................  
3. Has anti-fungal prophylaxis been prescribed? .................
   - Yes  
   - No  

**PART B:** Please complete retrospectively for events occurring since the previous cycle (or within 4 weeks of final cycle).

4. Was this cycle of chemotherapy given? .......................  
5. Number of trial medication capsules taken ..................
6. Did mucosal candidiasis occur?  
7. Did an infective episode occur?  
   (= fever and/or other clinical evidence of infection and/or empirical use of antibacterial therapy)  
   - Yes  
   - No  
8. Did a toxic event attributed to trial medication occur?  
   (If yes to question 8 - please describe in boxes)  
   - Yes  
   - No  

**OFF-STUDY SECTION**

- Please tick reason for discontinuation of Significant trial medication:  
  - Chemotherapy programme stopped early  
  - Planned chemotherapy programme completed  
  - Chemotherapy to be continued beyond 6 cycles  
  - Other 

- Date of discontinuation  

- *For these reasons, please continue to complete the On-Study Section for all cycles of chemotherapy given following discontinuation of trial medication.*

Following completion of chemotherapy, please send this form to:

The Significant Trial Office, Cancer Research UK Trials Unit, Institute for Cancer Studies, The Medical School, University of Birmingham, B15 2TT
The Significant Trial: Trial Entry Form

<table>
<thead>
<tr>
<th>Field</th>
<th>Details</th>
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</thead>
<tbody>
<tr>
<td>Patient surname</td>
<td></td>
</tr>
<tr>
<td>Patient forenames</td>
<td></td>
</tr>
<tr>
<td>Hospital number</td>
<td></td>
</tr>
<tr>
<td>Date of birth</td>
<td></td>
</tr>
<tr>
<td>Sex (M/F)</td>
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<tr>
<td>Age group</td>
<td></td>
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<tr>
<td>Telephone number</td>
<td></td>
</tr>
<tr>
<td>Consultant</td>
<td></td>
</tr>
<tr>
<td>Centre name</td>
<td></td>
</tr>
<tr>
<td>Code</td>
<td></td>
</tr>
</tbody>
</table>

Today's date

Entry Criteria: Please confirm that:
- Patient has a solid tumour or lymphoma
- Patient is about to commence the first cycle in a programme of chemotherapy
- Anticipated neutrophil nadir is less than 0.5 x 10^9 per litre
- There is no contraindication to the use of fluoroquinolone antibiotics
- There is no planned GCSF treatment or stem cell support
- Patient not currently receiving antibacterial therapy or prophylaxis
- Patient has either normal serum creatinine or GFR greater than 40ml per minute
- Patient is aged 18 or over
- Patient is not known to be HIV positive
- Patient has given written informed consent
- Patient has not previously participated in the significant trial

Note: Every box must be ticked for the patient to be eligible, otherwise discontinuous randomisation

Diagnosis of malignancy: What is the primary diagnosis?
- Small cell lung cancer
- Non-Hodgkin's lymphoma
- Breast cancer
- Hodgkin's disease
- Germ cell
- Other (please specify)

Chemotherapy regimen: Please ask for the following details
- Chemotherapy acronym (e.g., CHOP)
- Start date for chemotherapy
- Planned number of cycles in programme
- Length of cycle

Other relevant factors:
- Is chemotherapy being given in adjuvant setting?
- Is an indwelling venous catheter present?
- Has a previous programme of myelo-suppressive cytotoxic chemotherapy been given?
- Has previous radiotherapy been given which is likely to reduce tolerance to cytotoxic chemotherapy?
- WHO Performance status: [0-5]
  - 0: Normal activity
  - 1: Restricted to light work
  - 2: Ambulatory / self caring
  - 3: Bed or chair bound <50% waking hours
  - 4: Completely bed or chair bound, not self-caring

Microbiological evidence of infection:
- Organism(s)
- Site(s) of Culture
- Ciprofloxacin sensitive
- Levofoxacin sensitive

Treatment with anti-bacterial agent(s):
- Yes
- No

On completion, please send this form to:
The Significant Trial Office, CR UK Clinical Trials Unit, Institute for Cancer Studies, The Medical School, University of Birmingham, B15 2TT.
Simple Data Collection Encourages Recruitment

Total = 1565  Maximum = 70 patients

Monthly Recruitment
Cumulative Recruitment

Cancer Research UK Clinical Trials Unit
UNIVERSITY OF BIRMINGHAM
Are Simple Data Enough to Influence Clinical Practice?

**Febrile Episodes on Cycle 1**

7.9% vs 3.5%

Relative Risk = 0.44 (0.28, 0.68)

\( p < 0.001 \)

**Febrile Episodes Across Cycles**

15.2% vs 10.8%

Relative Risk = 0.71 (0.55, 0.92)

\( P = 0.01 \)
The Increasing Complexity of Clinical Trials

**Phase I**
- Dose-finding
- Aim: to find a safe dose of a new treatment and understand toxicities

**Phase II**
- Expansion
- Single arm
- Phase II RCT
- Aim: to determine if new treatment has sufficient efficacy to be worthy of further investigation

**Phase III**
- RCT
- Aim: to provide sufficient evidence on new treatment to potentially change clinical practice

**Early phase:**
- Phase I/II

**Late phase:**
- Randomised PII/III

Influence clinical practice
Phase I Dose-Finding Trials: Traditional 3+3 Cohort Rule-Based Design

- Objective: to seek Maximum Tolerated Dose (MTD) - minimum 6 pts at MTD
- Define a dose limiting toxicity (DLT)
- MTD = dose with ≤1/6 DLT where next highest dose has ≥2 DLT
- Start on the lowest dose d₁

Give dᵢ to 3 subjects

- 0 DLT: Proceed to dᵢ₊₁
- 1 DLT: Give dᵢ to 3 more subjects
- ≥2 DLT: STOP recommend dᵢ₋₁ as MTD

0 DLT: Proceed to dᵢ₊₁

≥1 DLT: STOP recommend dᵢ₋₁ as MTD
Example of Phase I Trial Design That Uses Statistical Modelling for More Accurate Dose-Finding

Combination Lenalidomide and Azacitidine: A Novel Salvage Therapy in Patients Who Relapse After Allogeneic Stem-Cell Transplantation for Acute Myeloid Leukemia

Charles Craddock, MD1,2; Daniel Slade, MSc2; Carmela De Santo, PhD2; Rachel Wheat, MSc2; Paul Ferguson, MD2; Andrea Hodgkinson, PhD2; Kristian Brock, MSc2; Jamie Cavenagh, MD2; Wendy Ingram, MD2; Mike Dennis, MD2; Ram Malladi, MD1; Shamyla Siddique, MPhil2; Francis Mussai, MD2; and Christina Yap, PhD2

Combination Dose of LEN With 75 mg/m² AZA

<table>
<thead>
<tr>
<th>Dose</th>
<th>(AZA only)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>2</td>
</tr>
<tr>
<td>Dose</td>
<td>2 (2.5 mg LEN)</td>
</tr>
<tr>
<td>Dose</td>
<td>0 (5 mg LEN)</td>
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<tr>
<td>Dose</td>
<td>1 (10 mg LEN)</td>
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<tr>
<td>Dose</td>
<td>2 (15 mg LEN)</td>
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<tr>
<td>Dose</td>
<td>3 (25 mg LEN)</td>
</tr>
<tr>
<td>Dose</td>
<td>4 (35 mg LEN)</td>
</tr>
</tbody>
</table>

Example of Phase I Trial Design Using the Continual Reassessment Method (CRM)

- **Cohort 1**: Dose 0: 75mg/m² Azacitidine + 5mg Lenalidomide; 0/3 DLT
- **Cohort 2**: Dose 1: 75mg/m² Azacitidine + 10mg Lenalidomide; 0/3 DLT
- **Cohort 3**: Dose 2: 75mg/m² Azacitidine + 15mg Lenalidomide; 0/2 DLT, 75mg/m² Azacitidine + 25mg Lenalidomide; 0/1 DLT *
- **Cohort 4**: Dose 3: 75mg/m² Azacitidine + 25mg Lenalidomide; 0/2 DLT
- **Cohort 5**: Dose 3: 75mg/m² Azacitidine + 25mg Lenalidomide; 1 (Fatigue + Rash) / 3 DLT
- **Cohort 6**: Dose 3: 75mg/m² Azacitidine + 25mg Lenalidomide; 1 (Deranged LFTs) / 3 DLT
- **Cohort 7**: Dose 3: 75mg/m² Azacitidine + 25mg Lenalidomide; 0/4 DLT

*Note: Risk of exceeding DLT threshold.*
Introduction of Randomisation to Phase II Trial Designs to Allow More Clinically Relevant Outcome Measures

Eligible Patients Randomised

STANDARD

NEW1

NEW2

NEW3

PFS Rate

PFS Rate

PFS Rate

0% Benchmark PFS rate

? 'Pick the winner'

100%

Primary outcome measure: progression-free survival (PFS) rather than objective response
Adaptive Designs in Phase III
Example: Multi-Arm Multi-Stage (MAMS) Phase III Trial

Phase III randomised controlled trial Comparing Alternative Regimens for escalating treatment of intermediate and high-risk oropharyngeal cancer

- Patients with intermediate and high-risk OPC recommended by MDT (18-70yrs, ECOG performance status 0-1 and fit for chemotherapy)
- Obtain Written Informed Consent for HPV/p16 Screening
- REGISTER PATIENT
  Log onto https://www.cancertrials.bham.ac.uk/CompARElive/
  (Emergency Registrations call CRCTU: 0121 414 9247 or 0121 414 5101)
  (9:00am-5:00pm Mon-Fri)
- Screening Assessment
  (patients screened for HPV/p16 immunohistochemistry via Central Laboratory Services)
  Send diagnostic biopsy sample to Department of Cellular Pathology, Royal Victoria Infirmary, Newcastle upon Tyne
- Confirm Eligibility
  (Confirmation of HPV/p16 status)
- If low-risk OPC consider other appropriate trial
- If intermediate or high-risk OPC enter patient into the CompARE Trial
- Obtain Written Informed Consent for Trial Entry
- Completion of Baseline Questionnaires and Sample Collection
  Questionnaires must be completed prior to patient being notified of treatment allocation
  - QoL Questionnaire (EORTC C30 and HN35)
  - Cost-effectiveness Questionnaire (EQ-5D)
  - Swallowing Assessment Questionnaire (MOADi)
  - Blood sample and oral fluid collection
RANDOMISE PATIENT
Stratified by eligibility to arms, risk (intermediate vs high-risk OPC) and treatment centre
Log on to https://www.cancertrials.bham.ac.uk/CompARElive/
(Emergency Randomisations call CRCTU: 0121 414 9247 or 0121 414 5101 (9:00am-
5:00pm Mon-Fri)

- **Arm 1**
  - Concomitant chemotherapy, 3-weekly cisplatin 100mg/m² or weekly 40mg/m² with radiotherapy using IMRT (70Gy in 35F)
  - Neck dissection as indicated by clinical and radiological assessment 3-months post treatment

- **Arm 2**
  - Induction chemotherapy (3 cycles at 3-weekly intervals: Docetaxel 75mg/m² + Cisplatin 80mg/m² + 5-FU 800mg/m²/day, daily for 4 days) +
  - Followed by Arm 1

- **Arm 3**
  - Dose-escalated radiotherapy using IMRT (64Gy in 25F) and concomitant cisplatin 100mg/m² or 40mg/m² +
  - Neck dissection as indicated by clinical and radiological assessment 3-months post-treatment

- **Arm 4**
  - Resection of primary +
  - Selective neck dissection followed by Arm 1

- **Arm 5**
  - Induction Durvalumab (1 dose, 1500mg) plus Arm 1
  - Followed by Adjuvant Durvalumab 1500mg every four weeks for 6 months

Patient Follow-up (at least 2 years)

Annual Follow-up (up to 5 years)
Changes in Trial Design to Move Towards Stratified Medicine

Objective: to stratifying patients according to biomarkers in order to select best treatments

Better understanding of biology enables prospective evaluation with biomarker-stratified RCT

Exploring potential biomarkers with retrospective correlative biomarker study within an RCT

B+ B-

Survival Time

NEW SoC

NEW SoC

NEW SoC

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Stratified Medicine Example: Correlative Biomarker study

Jonker DJ et al; Cetuximab for the treatment of colorectal cancer; NEJM 2007, 357: 2040-8

- Randomised controlled phase III trial (CO17)
- Advanced colorectal cancer expressing EGFR who had failed on prior chemotherapy
- Experimental drug: cetuximab, monoclonal antibody that targets EGFR
- Standard: best supportive care
- Primary outcome measure: overall survival time

HR=0.77
95%CI: (0.64, 0.92)
P=0.005
Stratified Medicine Example: Correlative Biomarker Study

Karapetis CS et al; K-ras mutations and benefit from cetuximab in advanced colorectal cancer; NEJM 2007, 357: 2040-8

HR=0.98
95%CI: (0.70, 1.37)
P=0.89

HR=0.55
95%CI: (0.41, 0.74)
P<0.001

Test for treatment-biomarker interaction: p=0.01
Better Understanding of Biology Creates New Era of Trial Designs For Stratified Medicine

Umbrella Phase II Platform Trial

Advanced NSCLC
N=315
March 15 - July 19
22 UK centres

NGS 28 gene panel test on diagnostic biopsy from SMP2

Stratification after progression on standard of care therapy

22 actionable biomarker groups

8 targeted therapies

ClinicalTrials.gov: NCT02664935
Practical Challenges of Running Trials in Stratified Medicine

- Biopsies
- Managing patient expectations about:
  - targeted treatments
  - negative biopsy results
  - limited time on drug
- Explaining and delivering complex designs to patients
- Tracking patients from biopsy to trial entry
- Slower set-up for complex trials
Challenges of Tracking Patients from SMP2 to National Lung Matrix Trial

4970 patients with samples sent
- 1068 patients with no NGS results
- 3904 patients with NGS results
  - 1075 patients with no tier 1/2
  - 2829 patients with a tier 1/2 aberration for NLMT
  - 1041 patients not eligible for arms A-H
- 1788 patients eligible for NLMT arms A-H
  - 1535 patients not recruited to NLM
    14% not suitable (toxicity, PS, ineligible)
    25% still on previous treatment
    28% died on previous treatment
- 253 patients recruited to NLMT arms A-H (June 2019)
Summary

- Evaluating impact of new treatments on quality of life / patient-reported outcomes is still an important aspect of clinical trials.
- Despite increasing complexity of trial designs, should data collection remain simple?
- Increasing complexity of trial designs for phase I, II and III:
  - enables more efficient evaluation of new treatments
  - enables molecular stratification of patients to optimise new treatments
  - presents logistical challenges for implementation
- Clinical research nurses are key to the successful delivery of clinical trials and should be an integral at the design stage.