Innovative trial design for older and frail populations

Matt Seymour
Medical Oncologist & Prof. GI Cancer Medicine, University of Leeds, UK.

SIOG Conference, Prague
14th November 2015

how do age, frailty & comorbidity affect cancer pharmacology?
some unanswered research questions:

How are the PK parameters of anticancer drugs affected by:

- chronological age
- age-related frailty
- comorbidity & comediations

some unanswered research questions:

How is the link from drug exposure (AUC) to toxicity (CTCAE grade) affected by:

- age-related frailty
- comorbidity
Pre- to post-treatment loss of cognitive function

Patients with below median baseline cognitive reserve*

Patients with above median baseline cognitive reserve*

* assessed using Wide Range Achievement Test (WRAT-3).

©2010 by American Society of Clinical Oncology
Ahles T A et al. JCO 2010;28:4434-4440

some unanswered research questions:

How is the impact of a given CTCAE level of toxicity affected by:

- chronological age
- age-related frailty
- comorbidity
- comedications
administered dose → pharmacokinetics → patient’s drug exposure → pharmacodynamics → efficacy and toxicity effects → impact → consequences for the patient

how to best treat the frail and/or elderly?
standard regimen full doses

supportive care alone

reduced doses

fewer drugs

different drugs

which trial designs to develop the evidence base?
Age distribution of patients in National Cancer Institute (NCI) adult cooperative group phase II and III trials (all cancers).

Hurria A et al. JCO 2014;32:2587-2594

age >65: 63% cancer cases
34% trial participants
not improving with time

So older patients who participate in “all ages” trials are exceptional

...and we can’t rely on subset analyses of these trials to tell us how to treat normal patients
We need clinical trials designed specifically for:

- the fit and very old
- the frail and ‘somewhat elderly’
- patients with comorbidities

...i.e. all the patients we often treat but don’t normally enrol in trials

Some challenges:

- How to define the population to recruit
  ➢ ...and then recruit them

- How to assess their health status
  ➢ ...in the oncology unit setting

- What are the right treatments to test?

- Do we know the relevant endpoints?
FOCUS2

Chemotherapy options in elderly and frail patients with metastatic colorectal cancer (MRC FOCUS2): an open-label, randomised factorial trial

Matthew T. Symmers, Lindsay T. Chapman, Margaret J. Wares, Gary Middlex, Alison L. Brown, Stephen T. Shepherd, M. Saud Al Hamary, Carole A. Macleod, Ruth M. Longley, on behalf of the FOCUS2 Investigators and the National Cancer Research Institute Colorectal Cancer Clinical Trials Group


Advanced CRC, no prior treatment
PS0-2, any age, GFR >30, bili ≤3x ULN

suitable for standard 1st-line clinical trial?

yes

no: frailty, age or both

enter the standard trial

enter FOCUS2

comprehensive health assessment

Randomisation
all chemotherapy doses 80% of standard

increase after 6 weeks to 100% if no major toxicity and doctor + patient agree

Outcomes: PFS, QoL

correlate outcomes with baseline for predictive analysis
Activities of daily living
- Nottingham: 21-point ADL scale
- 4 subscales (mobility; kitchen; domestic; leisure)

Global QL
- EQ5D: 5-point QL scale: mobility, self-care, activity, pain, mood

Symptoms
- QLQC30 scales for fatigue, nausea/vomiting, pain, dizziness, sleep disturbance, appetite, constipation and diarrhoea
- mean symptom score

Psychological
- HADS 14-point scale, anxiety and depression subscales

Overall Treatment Utility

patient’s view: was treatment worthwhile?

“overall treatment utility” (OTU)

did it have an objective anti-cancer effect?

was there major toxicity?

clinicians’ overall assessment of benefit?
after 12 weeks:

- **good OTU**
  - all of:
    - clinician 'benefit'
    - patient happy
    - no major toxicity

- **intermediate OTU**
  - either
    - clinician 'no benefit', but patient happy and no major toxicity
    - clinician 'benefit', but patient unhappy or major toxicity

- **poor OTU**
  - clinician 'no benefit'
  - and either
    - patient unhappy
    - major toxicity
  - or
    - patient has died

---

**Trial Design: 2x2 Factorial**

- **FU**
- **OxFU**
- **Cap**
- **OxCap**

Does addition of oxaliplatin improve efficacy?
- primary endpoint: PFS

Does using capecitabine instead of 5FU improve QoL?
- primary endpoint: overall QL score at 12 weeks
**Trial Design: does baseline health status predict OTU?**

Univariate comparisons
- to identify important baseline factors

Multivariate model
- towards developing a predictive tool
- include treatment allocation in model

---

**FOCUS2 main lessons:**

- **Feasibility:**
  - popular with patients and researchers
  - accrued 460 patients 6 months ahead of target

- **Main outcomes:**
  - PFS improvement just short of significant with oxaliplatin
  - Capecitabine did not improve QL

- **Overall Treatment Utility:**
  - 41% Good, 32% Intermediate, 27% Poor

- **Predictive model:**
  - Strongest baseline predictors are symptom score, PS (ADL functioning), liver-only metastases and allocation to oxaliplatin
Next step: gastroesophageal cancer

- Median age of diagnosis with inoperable disease = 77
- Median age in key trials = 63
- Many older or frail patients receive reduced-dose & non-standard chemo.
321GO Feasibility Study

45 frail and/or elderly patients
advanced gastroesophageal cancer

EOX = UK standard regimen for fit patients

RANDOMISATION

EOX (80%)   OX (80%)   X (80%)

‘Pick the winner’ design
PFS – 1 drug worse than 2 or 3

Fatigue – 2 drugs better than 1 or 3
Weight loss – 2 drugs better than 1 or 3

321-GO Feasibility conclusions

- 1-drug regimen: poor cancer control without improving tolerability/QL
- 3-drug regimen: poor tolerability/QL without improving cancer control
- 2-drug regimen selected for phase III trial
GO-2

- national phase III RCT
- minimum sample size 500 patients
GO2 objectives

- Find the **dose** of the 2-drug regimen to optimise outcomes
- Validate baseline patient characteristics which predict OTU (Overall Treatment Utility)
- Explore whether different dose levels are required to optimise OTU within brackets of baseline fitness.

GO2 trial

- **patients with inoperable GO cancer**
  - unfit/unsuitable for standard dose 3-drug regimen
- **patient/physician agreement**
  - is chemotherapy definitely required?
- **yes: 3-way randomisation**
- **no: 2-way randomisation**
- **OxCap Level A (100%*)**
- **OxCap Level B (80%)**
- **OxCap Level C (60%)**
- **BSC, no initial chemotherapy**

* percentages of oxaliplatin and capecitabine doses as used in standard EOX
GO2 trial

patients with inoperable GO cancer
unfit/unsuitable for standard dose 3-drug regimen

patient/physician agreement
is chemotherapy definitely required?

yes: 3-way randomisation
no: 2-way randomisation

minimum 500 patients

OxCap Level A (100%)
OxCap Level B (80%)
OxCap Level C (60%)

BSC, no initial chemotherapy

non-Inferior PFS
superior QL & OTU

superior OS (exploratory)
So...

- We need many more trials designed for older and frail patients
- We need basic research about age-dependent and comorbidity-dependent PK and PD
- We need better endpoints to assess the impact of treatment in this population (eg OTU)
- We need more research to validate baseline fitness tests to aid treatment decisions