Optimising RT dose for anal cancer - the development of three clinical trials in one platform

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Objective

- Previous phase III trials of squamous cell cancer of the anus have determined radiotherapy with concurrent Mitomycin C and 5FU as the standard of care.
- The RTOG 9811 and ACT2 trials demonstrated no improvement in cancer outcomes with neoadjuvant or maintenance cisplatin / 5FU.
- We developed IMRT guidance and clinical trials to address important research questions across the spectrum of patients presenting with loco-regional disease.

Methods

We formed a network of UK and international multi-disciplinary anal cancer investigators and trialists to:

- design clinical trials to address the following research questions:
  - **ACT3** – can a highly selective policy of involved field chemoradiotherapy (CRT) result in low locoregional failure (LRF) in small anal margin tumours treated by local excision?
  - **ACT4** – can reduced dose CRT using IMRT to the primary tumour, achieve an acceptably low rate of LRF in early stage anal cancer?
  - **ACT5** – can radiotherapy dose escalation reduce the LRF rate with acceptable toxicity in locally advanced anal cancer?

Results

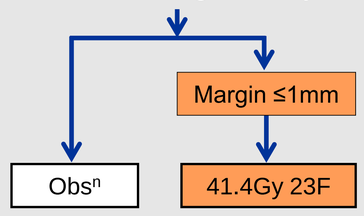
- The PLATO (PersonaLising rAdioTherapy dOse in anal cancer) is a platform trial comprising of the ACT3, 4 and 5 trials and funded by Cancer Research UK.
- Opened to recruitment in January 2017.
- **ACT3** (n=90) - non randomised phase II study that will evaluate a strategy of local excision for T1N0 anal margin tumours with selective post-operative involved field CRT using 41.4Gy in 23 fractions (F) and concurrent capecitabine, reserved for patients with margins <=1mm. An exact single-stage A'Hern design is used.
- **ACT4** (n=162) - randomised phase II trial (2:1) comparing reduced dose CRT with 41.4Gy in 23F to GTV with 50.4Gy in 28F using concurrent capecitabine for T1-2(<4cm)N0 disease with IMRT and elective nodal irradiation. An exact single-stage A'Hern design is used.
- **ACT5** (n=640) – seamless pilot (n=60)/phase II (n=140)/phase III trial (n=640 total) that will compare 53.2Gy with 58.8Gy and 61.6Gy using 28 F to GTV with either 5FU or capecitabine in T3/4 N1-3 disease. Toxicity and response will be reported for both the pilot and phase II components. Only one of the dose escalated experimental arms will be evaluated for the phase III component.
- Primary endpoint for each trial is 3 year LRF

PLATO – PersonaLising rAdioTherapy dOse for anal cancer

- Single clinical trial "platform" for three trials across the loco-regional disease spectrum.
- Single funding application; one protocol; one clinical trials unit; clinical leads for each trial; economic savings for this approach.

ACT3 trial

Eligibility
T1N0/Nx Anal margin locally excised



Trial leads – Muirhead and Renehan

Phase II trial N=90
Primary end point 3yr LRF

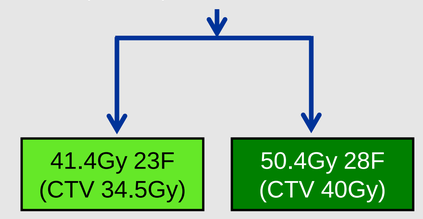
Radiotherapy – Involved field
- 3D Conformal
- GTV - 41.4Gy in 23F

Chemotherapy
- MMC 12mg/m^2 D1
- Cape 825mg/m^2 bid 5d/w

Statistics
- Efficacy can reach 90%
- Unacceptable efficacy <80%
- 90 patients are required (inc. 10% drop-out)

ACT4 trial

Eligibility
T1-2 (≤4cm) N0/x



Trial leads – Adams and Harrison

Randomised 2:1 Phase II N=162
Control is a calibration arm

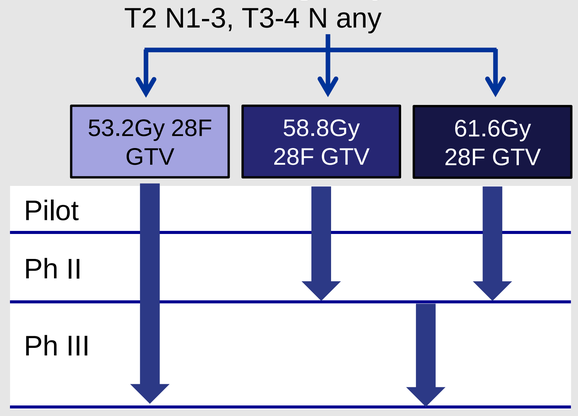
Primary end point 3yr LRF

Radiotherapy – IMRT
Chemotherapy
- MMC 12mg/m^2 D1
- Cape 825mg/m^2 bid 5d/wk

Statistics
- Efficacy can reach 90%; unacceptable efficacy < 80% (N=123)
- Planned p16+ sub-group analysis: 90% p16+ve and 90% suitable samples
- 162 patients (inc. 10% drop-out)

ACT5 trial

Eligibility
T2 N1-3, T3-4 N any



Trial leads – Hawkins and Sebag-Montefiore
Seamless Pilot / Phase II / Phase III N=677
Primary end point 3yr LRF

Radiotherapy – IMRT – CTV 40.0 Gy in 28F
Chemotherapy
- MMC & Cape or 5FU (centre policy)

Pilot n=60 – Assess acute toxicity and treatment compliance
Phase II n=140 – Acute toxicity, treatment compliance and Complete Response rate.
The most 'acceptable' SIB dose will be taken forward to phase III (i.e. 47 patients will not carry on to phase III.
Phase III n=640 Reduce LRF from 30% to 20% power 80% HR 0.63.

Imaging at baseline: Pelvic MR (ACT3,4,5); PET-CT strongly recommended (ACT4,5); CT chest abd pelvis (ACT4,5)

Imaging post CRT: Pelvic MR at 12 & 36 months (ACT3); at 3 & 6 months (ACT4,5); CT chest abd pelvis yrs 1,2,3 (ACT4,5)

Toxicity assessment: Acute toxicity CTCAE; Baseline and sequential PROMS (EORTC QLQ-C30 and QLQ-ANL27)

Conclusions

The PLATO trial platform can deliver:

- Different but linked research questions across the loco-regional disease spectrum with a personalised treatment approach.
- Efficiency using a single protocol and a single clinical trial funding application for three trials.
- Lead investigator roles for each trial
- For patient – single patient information sheet for the specific trial relevant to their disease stage
- The opportunity for translational and other sub-studies.

Sharing details of this concept can assist other investigators to develop similar future studies in other disease sites and allow parallel trials to be designed in other countries.

Further information

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