

The Development of an Umbrella Trial (PLATO) to Address Radiation Therapy Dose Questions in the Locoregional Management of Squamous Cell Carcinoma of the Anus.

Purpose/Objective(s)

Randomized controlled trials for patients with squamous cell carcinoma of the anus have been successfully performed, despite the rarity of the disease. The RTOG 9811 and ACT2 trials demonstrated no improvement in cancer outcomes when neoadjuvant or adjuvant cisplatin 5FU chemotherapy was used. To capture as many anal cancer patients as possible in future clinical trials, we developed an umbrella of trials testing efficacy and acceptable morbidity across different locoregional risk strata.

Materials/Methods

We formed a network of UK and international multi-disciplinary trialists and identified the following priorities:- i] the need for national consensus guidance for the introduction of intensity modulated radiation therapy (IMRT) based on the successful principles and fractionation used in the ACT2 protocol prior to future trials; ii] to evaluate a strategy using selective chemoradiation therapy (CRT) after local excision of anal margin tumors; iii] to evaluate reduced dose CRT to the primary tumor in order to limit late effects whilst maintaining elective nodal irradiation in early stage disease; iv] to evaluate dose escalated CRT in locally advanced T3/4 and N+ stage disease.

Results

The PLATO (personalizing radiotherapy dose in anal cancer) umbrella trial comprising of the ACT3, 4 and 5 trials is funded by Cancer Research UK and is due to commence recruitment in Q3 2016. The ACT 3 trial (n = 90) is a non-randomized phase II study that will evaluate a strategy of local excision for T1N0 anal margin tumors with selective postoperative involved field CRT using 41.4 Gy in 23 fractions (F) and concurrent capecitabine reserved for patients with margins ≤ 1 mm. An exact single-stage A'Hern design is used. The ACT4 trial (n = 162) is a randomized phase II trial (2:1) comparing reduced dose CRT with 41.4 Gy in 23F to GTV with 50.4 Gy in 28F using concurrent capecitabine for T1-2(<4cm)N0 disease. An exact single-stage A'Hern design is used. The ACT5 trial (n = 677) is a seamless pilot (n = 60)/phase II (n = 140)/phase III trial (n = 672 total) that will compare 53.2 Gy with 58.8 Gy and 61.6 Gy using 28 fractions to GTV with either 5FU or capecitabine in T3/4 N1-3 disease. Only one of the dose escalated experimental arms will be evaluated for the phase III component. The primary end point for each trial is 3 year locoregional failure.

Conclusion

The PLATO trial concept allows different research questions across the locoregional disease spectrum to be addressed efficiently using a single protocol and clinical trial funding application. This type of trial design is increasingly important in the era of personalized medicine and the need for clinical studies to address different research questions within the same disease. Sharing the details of this concept should assist other investigators to develop similar future studies.