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Standard or high dose chemoradiotherapy, with or without the protease inhibitor nelfinavir, in patients with locally advanced pancreatic cancer: the phase 1/randomised phase 2 SCALOP-2 trial

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ABSTRACT

Background: The multi-centre two-stage SCALOP-2 trial (ISRCTN50083238) assessed whether dose escalation of consolidative chemoradiotherapy (CRT) or concurrent sensitization using the protease inhibitor nelfinavir improve outcomes in locally advanced pancreatic cancer (LAPC) following four cycles of gemcitabine/nab-paclitaxel.

Methods: In stage 1, the maximum tolerated dose (MTD) of nelfinavir concurrent with standard-dose CRT (50.4Gy in 28 fractions) was identified from a cohort of 27 patients. In stage 2, 159 patients were enrolled in an open-label randomized controlled comparison of standard versus high dose (60Gy in 30 fractions) CRT, with or without nelfinavir at MTD. Primary outcomes following dose escalation and nelfinavir use were respectively overall survival (OS) and progression free survival (PFS). Secondary endpoints included health-related quality of life (HRQoL).

Results: High dose CRT did not improve OS (16.9 (60% confidence interval, CI 16.2-17.7) vs. 15.6 (60%CI 14.3-18.2) months; adjusted hazard ratio, HR 1.13 (60%CI 0.91-1.40; p=0.68)). Similarly, median PFS was not improved by nelfinavir (10.0 (60%CI 9.9-10.2) vs. 11.1 (60%CI 10.3-12.8) months; adjusted HR 1.71 (60%CI 1.38-2.12; p=0.98)). Local progression at 12 months was numerically lower with high-dose CRT than with standard dose CRT (n=11/46 (23.9%) vs. n=15/45 (33.3%)). Neither nelfinavir nor radiotherapy dose escalation impacted on treatment compliance or grade 3/4 adverse event rate. There were no sustained differences in HRQoL scores between treatment groups over 28 weeks post-treatment.

Conclusions: Dose-escalated CRT may improve local tumour control and is well tolerated when used as consolidative treatment in LAPC but does not impact OS. Nelfinavir use does not improve PFS.

KEY WORDS

Pancreatic cancer; Chemoradiotherapy; Nelfinavir; Dose escalation; Survival; Outcomes; Toxicity; Health-related quality of life

INTRODUCTION

Pancreatic cancer is the seventh leading cause of cancer-related death worldwide, with a mortality to incidence ratio that exceeds 90%[1]. Around a third of patients present with inoperable locally advanced pancreatic cancer (LAPC), which is broadly defined by an absence of metastases but extensive tumour contact with local vasculature that jeopardizes curative resection[2]. There is uncertainty regarding the optimal management of patients with LAPC, although primary systemic therapy is established as the standard of care, due at least in part to a high propensity for early metastatic spread[3-5].

Establishing local tumour control is important for increasing the proportion of patients eligible for a potentially curative resection as well as for reducing rates of local progression, which is a key cause of morbidity and which reportedly causes around 30% of deaths in this cohort[6,7]. Correspondingly, European and American guidance suggest that CRT can be considered as consolidation therapy in symptomatic patients and in those who do not have progressive disease following upfront systemic therapy[8,9]. Pancreatic cancers are, however, radioresistant and outcomes following CRT remain disappointing, with local failure rates persisting at 30-40% and a complete radiological or pathological response realized in less than 5% of patients[10-12].

A greater biological effect from radiotherapy may be achieved by dose escalation, or by optimizing strategies for tumour radiosensitisation. There has, however, been uncertainty regarding the feasibility of delivering higher radiation doses in the context of CRT given a relationship between treatment toxicity and dose to surrounding organs at risk (OARs) such as the stomach and duodenum[13,14]. There are also no currently approved sensitization strategies beyond the use of cytotoxic chemotherapy. However, preclinical data suggest that the antiretroviral protease inhibitor nelfinavir promotes radiosensitisation of pancreatic cancer cells via the downregulation of phosphorylation of Akt serine 473, which reduces activity of the PI3K/Akt pathway, even in cells that have a mutation of *KRAS*[15-18]. This is commonly overactive in pancreatic cancers but not in normal tissues, thereby theoretically allowing for the specific radiosensitisation of tumour cells. Adding to this, at the time of trial initiation two early phase studies evaluating nelfinavir use with pancreatic radiotherapy had shown promising outcomes, including a 50% complete radiological response rate and 1-year survival of 73%, without compromising toxicity[19,20].

Given this, in the Systemic therapy and Chemoradiation in Advanced LOcalised Pancreatic cancer (SCALOP)–2 trial reported here we sought to evaluate the safety, toxicity and efficacy of radiotherapy dose escalation and nelfinavir, alone and in combination, in patients with LAPC managed with capecitabine-based CRT.

METHODS

Study design and patients

The SCALOP-2 trial comprised of two stages. These are fully outlined in the study protocol, which has been published previously and which is included here as **Appendix 1**[21]. The first single-arm safety run-in stage focused on finding the maximum tolerated dose (MTD) of nelfinavir when used concurrently with standard dose (50.4Gy in 28 fractions) capecitabine-based CRT. The second stage commenced once the primary objective of stage 1 had been met and was a multi-centre, open-label, randomised 2×2 factorial + 1, phase II study that sought to answer two questions. Firstly, whether high dose capecitabine-based CRT (60Gy in 30 fractions) improves overall survival (OS) when compared to standard dose CRT and, secondly, whether the addition of nelfinavir at its MTD to standard- or high-dose CRT improves progression free survival (PFS).

Briefly, we recruited patients of at least 18 years in age who were of World Health Organisation (WHO) performance status (PS) 0 or 1 and who had histologically or cytologically proven pancreatic carcinoma. To be registered for the trial, patients were required to have computed tomography (CT) or positron emission tomography (PET)-CT imaging of the thorax, abdomen and pelvis in the six weeks prior to commencing treatment. The primary pancreatic lesion was required to measure 6cm or less by imaging, with the disease classified by a site-specialist multidisciplinary team as locally advanced and inoperable but non-metastatic using National Comprehensive Cancer Network criteria.

All patients had to provide written informed consent prior to registration, after which they would proceed within 21 days to commence an induction gemcitabine/nab-paclitaxel (gem/nabP) doublet. Eligibility for CRT was confirmed in those with responding or stable disease based on cross-sectional imaging, for whom the tumour could be encompassed within a radical radiotherapy treatment volume and who remained at a WHO PS of 0 or 1. In stage 2, patients were randomised once confirmed eligible.

The study was approved by the South Central – Oxford A Research Ethics Committee and by the UK Medicines and Healthcare Products Regulatory Agency. Data are reported here in compliance with the CONsolidated Standards of Reporting Trials (CONSORT) statement[22].

Information relating to study governance and trial oversight is provided in **Appendix 2**, as is information on randomisation and masking as well as the study procedures.

Statistical analysis

All analyses were undertaken in accordance with a pre-specified statistical analysis plan. Stage 1 used the rolling-six design to establish the recommended dose of nelfinavir to be administered with CRT in stage 2. Participants who fulfilled the criteria for evaluability, including all participants with dose limiting toxicities (DLTs), were assessed. DLTs were defined as per CTCAE v4.03 as any grade 4 or above toxicity, any non-haematological grade 3 nelfinavir or treatment-related adverse event (AE) deemed clinically significant by the investigator, an inability to tolerate at least 20 fractions of RT due to an AE or a serious AE requiring a pause in RT of at least 14 days.

In stage 2, the two primary endpoints were PFS by nelfinavir arms (A+C vs. B+D), and OS by CRT arms (C+D vs. A+B). The estimated sample size was 168 recruited based on an assumption from SCALOP trial data that 65% would not progress through induction therapy and that 96 patients would therefore be randomised to arms A to D[11]. This was the final revised calculation following the decision to close arm E and would detect a hazard ratio (HR) of ≤0.65 with 80% power and one-sided alpha=0.2, accounting for 10% loss to follow-up for the PFS outcome and negligible loss to follow-up for the OS outcome. This calculation was based on an assumed median PFS of 12 months in the no nelfinavir arm and median OS of 15 months in the 50.4Gy arm. Secondary endpoints were PFS and one-year OS by RT assignment, OS by nelfinavir assignment, safety (as per CTCAE, version v4.03), resection rate, compliance with CRT, one-year local control, CA19-9, disease response at 6 weeks post-CRT treatment, and HRQoL.

Analyses were undertaken using Stata Statistical Software V15.1 (Stage 1) and V16.1 (stage 2), (StataCorp. College Station, TX: StataCorp LLC), and R version 3.3.2 (Stage 1). Analyses for stage 2 were done according to the intention-to-treat principle such that all randomised patients were included in their allocated group. Per-protocol analyses were conducted for the primary outcomes and included participants who received all prescribed fractions of CRT and, for arms A and C, at least 70% of nelfinavir. Safety analyses included all participants who received at least one dose of any protocol-specified treatment. For comparisons between CRT arms, all randomised patients were included. For comparisons between nelfinavir arms, concurrently randomised patients up to the date (26th February 2020) of arm A and C closure were included. Additional information relating to statistical analyses is included in **Appendix 2.**

This trial is registered with International Standard Randomised Controlled Trial Number (ISRCTN) 50083238.

Role of the funding source

Cancer Research UK and Celgene Ltd had no role in study design, data collection, data analysis, data interpretation, the writing of the study report or the decision to submit for publication. SM, CQ and CMJ had full access to the study data. SM had final responsibility for the decision to submit for publication.

RESULTS

Overview

For stage 1, 27 participants were registered from nine participating sites (**Supp. Table 1**) between March 2016 and May 2017. Eighteen of these were considered evaluable for MTD (**Supp. Fig. 1**). Recruitment for stage 2 took place in 23 sites between August 2017 and March 2020. Arm E was initially planned as a systemic therapy calibration arm but was closed to favour recruitment to arms A-D, with relevant systemic therapy calibration data provided through publication of the LAPACT trial[23]. Study centre was dropped as a minimisation factor as recruiting centres at this stage exceeded 20 (**Supp. Table 1**). Trial recruitment was temporarily halted in February 2020 following advice from the data safety and monitoring committee (DSMC) and trial steering committee (TSC) to close nelfinavir treatment arms (A and C) relating to lack of efficacy, as outlined in **Appendix 2**. The coronavirus disease 2019 (COVID-19) pandemic significantly interrupted UK trials activity in March 2020 and as the SCALOP-2 trial was due to close to recruitment in May 2020, did not reopen. Patients already recruited proceeded to randomisation to the remaining open arms, B and D.

In total, 159 patients were recruited to stage 2, 150 of whom commenced gemcitabine/nabP. As outlined in **Supp. Table 2**, 33 (20.8%) of these did not reach the randomisation time point. Of the remaining 126 who were assessed for eligibility, 106 (84.1%) patients were randomised; 91 of whom were allocated to arms A-D (**Figure 1**). The reasons for ineligibility for randomisation are provided in **Supp. Table 2.** Whilst recruitment of 96 patients to arms A-D had been planned to capture 62 PFS events and 62 deaths, 75 PFS events and 64 deaths were seen with 91 patients.

Baseline characteristics

The baseline characteristics of patients enrolled in stages 1 and 2 are shown in **Supp. Table 3** and **Table 1**, respectively. Sex, performance status and the primary pancreatic tumour site (head versus body/tail) do not appear well balanced between the stage 2 arms. Median baseline CA19-9 level

appears to show variation between treatment arms but interquartile ranges are large. Relevant missing data items for stage 2 are summarised in **Supp. Table 4**.

Compliance & safety

Data relating to treatment compliance and safety are included in **Appendix 2.**

Primary endpoints

OS was assessable in all 91 randomised patients (**Fig. 2A; Supp. Figs. 2A & 2B**). Thirty-one (68.9%) of the 45 patients in the standard dose CRT arm died, compared with 33 (71.7%) of the 46 patients in the high-dose CRT arm. This translated to respective median OS of 15.6 (60%CI 14.3-18.2) months and 16.9 (60%CI 16.2-17.7) months (log-rank p= 0.68, adjusted HR 1.13 (60%CI 0.91-1.40; adjusted p=0.68), adjusted p-value 0.68), and 1 year survival of 75.3% (60%CI 69.3-80.2) and 73.0% (60%CI 67.0-78.2)). PFS was assessable in all 76 patients randomised before the closure of arms A and C (**Fig. 2B; Supp. Figs. 3A & 3B**). Three patients died without progression. Thirty two (84.2%) of the 38 patients who did not receive nelfinavir had a progression event compared with 35 (92.1%) of the 38 patients who did receive nelfinavir; translating to respective median PFS of 11.1 (10.3-12.8) months and 10.0 (9.9-10.2) months (log-rank p=0.98, adjusted HR 1.71; 60%CI 1.38-2.12; adjusted p=0.98). Per-protocol analyses for OS and PFS were consistent with these data (**Supp. Table 11**). Sensitivity analyses did not identify an interactional effect from the factorial design of the trial for either of the primary endpoints (**Supp. Table 12**).

Secondary disease control endpoints

A summary of secondary endpoints relating to disease control is provided in **Table 4**. No difference was seen in PFS by radiation dose or OS by nelfinavir usage. A greater proportion of patients had stable or responding disease at 6-weeks post CRT with high-dose radiation than with standard dose radiation (n=29/46; 63.1% vs. n=22/45; 48.9%). In a post-hoc analysis of patients with evaluable imaging, this translated to a significantly greater disease control rate for high-dose versus standard dose radiation (29/35, 82.9% vs. 22/36, 61.1%; chi-square p=0.04). Similarly, the rate of local progression at 12 months was lower with high-dose CRT (n=11; 23.9%) than with standard dose CRT (n=15; 33.3%), whilst 3/12 (25.0%) patients in the high dose arm compared with 7/11 (63.6%) in the standard dose CRT arm died after local progression (**Supp. Table 13**)**.** The proportion of patients with local

progression by 12 months was similar with (n=12/38; 31.6%) or without (11/53; 28.9%) nelfinavir. Despite this, a lower proportion of patients treated with nelfinavir were progression free at 12 months (47.4%; n=18/53 vs. 28.9%; n=11/38) due to a higher rate of metastatic spread with nelfinavir (39.5%; n=15/38 vs. 23.7%; n=9/53). Resection rates were similar between standard and high dose CRT, and with or without nelfinavir use. There was no difference between arms in disease response rates or CA19-9 level (**Table 4**).

Survival and disease control data from arm E and the observation cohort are respectively presented in **Supp. Table 14** and **Supp. Table 15.**

Quality of life measures

A summary of data availability for each of the three HRQoL measures at each of the five assessed timepoints is provided in **Supp. Table 16**. The proportion of patients for whom data was available is higher for assessments up to six weeks post-CRT than after this timepoint. At the end of CRT, mean Global Health Status (GHS) score was respectively 66.7 (interquartile range, IQR 50,83.3) versus 75.0 (IQR 58.3, 83.3) for standard and high dose CRT, and 66.7 (IQR 50,83.3) versus 66.7 (58.3, 83.3) with and without nelfinavir. The EQ5D score at this timepoint was respectively 0.75 (IQR .66,.91) versus 0.84 for standard versus high dose CRT, and 0.8 (IQR 0.57, 0.88) versus 0.8 (IQR 0.66,0.91) with and without nelfinavir. Both scores were consistent across timepoints to week 6 post-CRT, at which point a fall in EQ-5D-5L but not the GHS score is seen across all studied cohorts (**Supp. Figs. 4-7**). No difference was seen in EORTC QLQ-C30 or EQ-5D-5L score between standard and high dose CRT (**Supp. Table 17 & 18, respectively**)**,** and by nelfinavir usage (**Supp. Table 19 & 20, respectively**)**,** at any of the assessed timepoints. Data relating to specific symptoms are provided in Appendix 2.

DISCUSSION

In the SCALOP-2 trial, neither radiotherapy dose escalation nor the putative radiosensitizer nelfinavir resulted in improved OS or PFS in patients with LAPC managed with capecitabine-based CRT. Radiotherapy dose escalation and nelfinavir were nevertheless well tolerated and the use of high-dose CRT correlated with numerically lower rates of local tumour progression. This was supported, albeit in a post-hoc analysis, by significantly better disease control six weeks after high-dose CRT.

The role of radiotherapy in the management of LAPC remains controversial. The LAP07 trial demonstrated that when used in patients with controlled disease following four months of

gemcitabine-based induction chemotherapy, three-dimensional conformal consolidation capecitabine-based CRT (54Gy in 30 fractions) was well tolerated and associated with lower rates of local progression (32% vs. 46%; p=0.04)[12]. The use of CRT did not, however, translate to an improvement in median OS. This is perhaps unsurprising given that this cohort is at high risk of developing metastatic disease[7]. In LAP07 enhanced local control resulting from CRT nevertheless resulted in a longer interval to the next line of systemic therapy, which with an improvement in symptoms from locally progressive disease is postulated to result in improved HRQoL[12,24,25].

Here, rates of local progression at twelve months were 23.9% in the high dose CRT arm compared to 33.3% in the conventional dose arm. Although the small numbers do not allow formal statistical comparison, this increase in local control lends support to a growing body of evidence for a radiation dose-response relationship in this malignancy, albeit in the context of patients who receive induction chemotherapy[26,27]. This apparent improvement in local control with high-dose CRT did not, however, translate to a sustained benefit in any of the assessed HRQoL measures when assessed up to seven months after completion of treatment. It is uncertain why this discrepancy exists, though the use of prolonged induction regimes such as those shown here may allow for prior optimization of cancer-related symptoms and may also select for patients with less aggressive disease biology. Regardless, CRT was well tolerated in this study and there was no additional radiation related toxicity in the high dose arm, providing strong evidence for the safety and tolerability of dose escalation using IMRT in the context of concurrent CRT. Indeed, whilst shorter term pancreatic pain and bowel habit appeared worse with higher-dose treatment, there was no detriment with respect to indigestion or eating related items despite previous modelling raising concerns for gastroduodenal toxicity from dose-escalated radiotherapy regimes[13,14]. Patients who had received high-dose CRT also reported improved body image and sexuality.

The use of stereotactic body radiotherapy (SBRT), which is usually delivered in 3-5 daily or alternate day fractions, offers an alternative to CRT and is rapidly replacing CRT as the preferred consolidation regimen in patients with LAPC[28,29]. The advantage to local control seen with high-dose CRT here is likely to extrapolate to the high radiation doses deliverable via SBRT. It may be that the more limited burden on patients from these shorter treatment regimens favours their use to achieve better local control, particularly if it allows for longer breaks in the use of systemic therapies or a reduction in local symptoms. SBRT may also achieve a lower incidence of radiation-induced lymphopenia as well as tumour-related complications such as pain and jaundice when compared to CRT[24,30].

An alternative means to improving the biological effect of radiotherapy is to identify efficacious drug radiotherapy combinations that overcome the intrinsic radioresistance of pancreatic cancer. The

antiretroviral protease inhibitor nelfinavir has shown promise as a potent radiosensitizer in preclinical models representing numerous malignancies[31]. This includes pancreatic cancer, in which its proposed mechanism of action centres on inhibition of the PI3K-Akt-mTOR pathway induction of endoplasmic reticulum stress and the unfolded protein response, vascular remodelling and tumour reoxygenation[18-20,32,33]. Outcomes with nelfinavir were nevertheless disappointing. It is not clear why this is the case but the failure to repurpose nelfinavir in this study unfortunately reflects far broader challenges with translating promising novel drug-radiotherapy combinations from the bench to the bedside[34].

It is important to note that in this study, data relating to subsequent lines of treatment were available for only 41-58% of patients, with a suggestion of differences between treatment arms. The impact of this on the present data is unclear. Additionally, data relating to local tumour progression, which was not a primary outcome, may be influenced by relatively small patient numbers. The completeness of HRQoL data also falls over time, potentially opening data to influence from responder bias. Further, assessment of response by RECIST was not mandated, which may have led to some variation in response assessments.

It is also important to note that the systemic standard of care for patients with LAPC would now be regarded as FOLFIRINOX, rather than the induction gemcitabine/nabP doublet used here. This does not detract from the comparisons drawn between high and standard dose radiotherapy, nor those relating to nelfinavir use. One randomised phase II study comparing modified FOLFIRINOX versus gem/nab-paclitaxel in LAPC has demonstrated comparable efficacy between the regimens with lower GI toxicity in the gem/nab-paclitaxel arm[35]. CONKO-007, a randomized phase III study comparing chemotherapy alone (FOLFIRINOX-77%; Gemcitabine-23%) with or without consolidation CRT has been reported in abstract form only[36]. The 12 month PFS and OS in CONKO 007 (56% and 71% respectively) is comparable to that seen in this study as well as in the original SCALOP trial which used gemcitabine-capecitabine as the induction regimen; suggesting that the choice of induction chemotherapy may not necessarily influence survival outcomes.

This study is nevertheless the first randomized, prospective, comparison to report on CRT dose escalation and nelfinavir use, with comprehensive corresponding data presented here for their safety, toxicity and HRQoL. High-dose CRT is very well tolerated and appears to positively impact on local control. This favours further evaluation of the impact of radiotherapy dose escalation in the setting of LAPC, including using contemporary techniques such as SBRT.

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CONTRIBUTORS

SM, CQ, CNH, PSV and RS contributed to the design and development of the trial. SM, CQ, RS, NP, JH, PP, PSV and BT contributed to the writing and review of the protocol. SM, CQ, RS, NP, JH, PSV, BT and PP were involved in the day-to-day running of the trial. SM, CQ, CMJ, JH and PSV were responsible for statistical analysis and data interpretation. SM, JAB, GR, SF, HSW, TVA, DH, RR, MSB, CNH, DSM, TSM, MAH and PC contributed to the recruitment of patients and study management. SM, CQ, CMJ, NP, JH, PSV, CNH and BT contributed to the analysis and interpretation of data. CQ and CMJ provided data representations. CMJ drafted the first version of the manuscript. All authors have contributed to, seen and approved the final draft of the manuscript.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

DATA SHARING

The data collected for the study, including individual participant data and a data dictionary defining each field in the set, will be made available to researchers on request to the study team and with appropriate reason, via octo-enquiries@oncology.ox.ac.uk. The shared data will be de-identified participant data and will be available for 5 years following publication of the study. Data will be shared with investigator support, after approval of a proposal and with a signed data access agreement.

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