The impact of gemcitabine chemotherapy and 3D conformal RT/5FU on quality of life of patients managed for pancreatic cancer

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Quality of life in patients with pancreatic cancer.

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CONFLICT OF INTEREST NOTIFICATION

Dr. Reece was an employee of and Dr. Goldstein has acted as a consultant for Eli Lilly and Company. No other authors have a conflict of interest to disclose.

SUMMARY

A prospective, longitudinal assessment of Quality Of Life (QOL) was undertaken in 41 inoperable locally advanced and 22 resected patients with pancreatic cancer at high risk of local relapse as part of a Phase II study of a specific 3D conformal radio-chemotherapy sandwich technique to treat pancreatic cancer. The patterns of change in global QOL scores differed between the patient cohorts. For both groups, the treatment protocol was well tolerated and did not have a negative impact on patients' global QOL.

ABSTRACT

PURPOSE: The role of chemo-radiotherapy for pancreatic cancer in both the definitive and post-operative settings is controversial, with concerns about its potential impact on Quality Of Life (QOL) limiting its use. The aim of this paper was to report the QOL results of patients receiving treatment for pancreatic cancer.

METHODS AND MATERIALS: Eligible patients (n = 41 locally advanced, n = 22 post-surgery) entered the B9E-AY-S168 study and received one cycle of induction gemcitabine (1000 mg/m^2 weekly ×3 with one week break) followed by 3DCRT (54Gy locally advanced and 45Gy post-surgery) and concomitant continuous infusion 5FU (200mg/m^2/day throughout RT). After four weeks, patients received an additional three cycles of consolidation gemcitabine chemotherapy. Patients completed the EORTC QLQ–C30 and QLQ–PAN26 questionnaires at baseline, before RT/5FU, end of RT/5FU, before consolidation gemcitabine and at treatment completion.

RESULTS: The patterns of change in global QOL scores differed between groups. In the locally advanced group global QOL scores were +13, +8, +3 and +1 compared with baseline before RT/5FU (p = .008), end of RT/5FU, before consolidation gemcitabine and at treatment completion, respectively. In the post-surgery group, global QOL scores were −3, +4, +15 and +17 compared with baseline at the same time-points, with a significant improvement in global QOL before consolidation gemcitabine (p = .03). No significant declines in global QOL were reported by either cohort.

CONCLUSIONS: This study demonstrates that global QOL and associated function and symptom profiles for pancreatic chemo-radiotherapy differ between locally advanced and post-surgery patients, likely to be due to differences in underlying

disease status. For both groups, the treatment protocol was well tolerated and did not have a negative impact on patients' global QOL.

KEYWORDS: pancreatic cancer, gemcitabine, RT/5FU, EORTC QLQ–C30, QLQ–PAN26

INTRODUCTION

Pancreatic cancer remains a most difficult cancer to treat with an overall five-year survival rate of 4% (1). Outcomes are best in patients with localized disease who undergo major resection with clear margins, but the median survival is modest at 20 months. Adding modern adjuvant chemotherapy marginally increases this to between 22 months (2) and 23.6 months, as shown in a recent European Study Group for Pancreatic Cancer Phase III trial (ESPAC-3)(3).

The role of adjuvant Radiation Therapy (RT) in prolonging Overall Survival (OS) is equivocal as some trials have suggested poorer OS with chemo-radiotherapy compared with no adjuvant treatment (4, 5), although the radiation therapy techniques used have been deemed outdated (6). In patients with locally advanced inoperable tumors, modern 3D Conformal RT techniques (3DCRT) combined with chemotherapy result in median OS between 14.5 months (7) and 15 months (8). Our recent work showed that a specific 3DCRT sandwich technique is safe both as a definitive treatment for inoperable locally advanced pancreatic cancer patients and as an adjuvant treatment for resected patients with high risk features for subsequent local relapse (9, 10). The encouraging survival outcomes of the definitive treatment (10) supported further collaborative development (11), whilst the case for adjuvant treatment for patients at high risk of local recurrence (margin positive) remains unclear (8).

Given that OS is so poor, understanding how these intensive interventions impact on patients' Quality Of Life (QOL) is central to helping patients make informed decisions about the most appropriate treatment intervention. Here, we report the

longitudinal QOL results assessed with EORTC QLQ–C30 (12) and QLQ–PAN26 (13) questionnaires.

METHODS AND MATERIALS

Eligibility criteria

All patients provided written informed consent. Two independent cohorts of patients were prospectively recruited into the study (B9E-AY-S168). The recruitment strategy is described elsewhere (10). Eligibility criteria included a histological or cytological diagnosis of pancreatic adenocarcinoma in the head or body of the pancreas, with metastatic disease excluded on whole body CT. Resected patients were required to have surgically defined risk factors for local recurrence present, including any of the following: positive histological margins; close margins (involved or presence of any tumor to within 5 mm of the edge of the specimen); positive nodal status on biopsy; or lymphovascular invasion.

Study design

Eligible patients received one cycle of induction gemcitabine chemotherapy (<8 weeks post-surgery for resected patients), followed by radiotherapy and concomitant continuous infusion 5FU, four weeks of rest and then additional three cycles of consolidation gemcitabine chemotherapy (Figure 1). Each gemcitabine cycle consisted of a dose of 1000 mg/m^2 administered weekly for three consecutive weeks followed by a week of rest. Gemcitabine was given by intravenous infusion over approximately 30 minutes. 5FU was given as a continuous intravenous infusion, with a dose of 200 mg/m^2/day, seven days a week, commencing on the first day of RT and continuing until RT completion. The radiation dose prescribed was 54Gy in 30 fractions for the locally advanced and 45Gy in 25 fractions for the post-surgery cohort, each given in accordance with International Commission on Radiation Units

and Measurements (ICRU) principles (14). The full details of dose adjustments in chemotherapy and radiotherapy for toxicity are described elsewhere (10).

Quality of life

QOL was first assessed <14 days before commencement of gemcitabine (baseline). Subsequent QOL assessments were timed to compare the effect of each treatment component on QOL relative to baseline to identify the overall net effect of treatment to that time-point: time-point 1, end of induction gemcitabine immediately prior to RT/5FU (to assess the acute toxicity and/or symptom relief attributable to induction gemcitabine chemotherapy); time-point 2, end of final week of RT/5FU (to assess acute toxicity); time-point 3, four weeks following RT/5FU immediately before consolidation gemcitabine (to identify ongoing toxicity of chemo-radiation); and time-point 4, at the completion of the program.

Assessments comprised two self-administered questionnaires; the EORTC QLQ–C30 (Version 2.0) and the disease-specific QOL module for pancreatic cancer QLQ–PAN26. EORTC QLQ–C30 is a 30-item questionnaire designed to assess the QOL of cancer patients, comprising a global health and QOL scale, five functional scales, three symptom scales and several single-item symptom measures (12). In this instrument, higher scores on the functional subscales indicate better functioning, whereas higher scores on the symptom scales indicate worse symptoms. Total scores for each subscale were summed based on the EORTC QLQ–C30 scoring manual (15) and converted to range between ‘0’ and ‘100’. The QLQ–C30 questionnaire has been widely used in cancer patients with acceptable reliability and validity (12). The QLQ–PAN26 is a supplementary module specific to pancreatic cancer and contains 26

questions covering seven disease and treatment-related domains and ten single items assessing a range of symptoms (13).

Data analysis

Analyses were conducted independently for each patient cohort. Investigation of the differences in QOL domains across cohorts were not performed as this was not the primary objective of the study. Differences between mean QOL scores at each time-point and the baseline QOL scores were calculated for each subscale to investigate the cumulative effect of treatment. The global QOL domain was selected to represent an overall effect summary measure and all other individual scales were analyzed to provide explanatory insight for changes in global QOL. To aid interpretation, the direction of change in mean differences was adjusted to be consistent between subscales i.e. improvements in function or symptoms were scored positively, whilst worsening function or symptoms were scored negatively. Additionally, to facilitate pattern comparisons across time-points, QOL items were ranked according to the magnitude of change from baseline. Statistical significance was calculated using paired t-tests with a significance level of $p < .05$. Clinically important change was defined as a change in mean QOL score greater than ten percentage points for an individual scale (16). Patients who progressed did not complete further questionnaires. Given the multiple endpoints and modest patient numbers, we describe only the overall effects of QOL and have not explored associations with common covariates; however, no major postoperative complications occurred and stenting was only required in two patients during the study (9).

RESULTS

Baseline patient characteristics

Sixty-three patients were enrolled in the study, 41 in the locally advanced and 22 in the post-surgery cohort. Patients in the post-surgery cohort were younger, but otherwise the characteristics at baseline were similar between the two groups (Table 1).

Cancer survival

The median survival for patients in the locally advanced cohort was 11.7 months, median time to progression was 7.1 months and median time to failure of local control was 11.9 months. For the post-surgery cohort, the median survival was 15.6 months, median time to progressive disease after surgery was 11.0 months and median time to failure of local control was 32.9 months.

Questionnaire return

Questionnaire return compliance was 94% (59/63) at baseline; 61% (37/61) at time-point 1, 44% (27/61) at time-point 2; 53% (32/60) at time-point 3; and 53% (32/60) at time-point 4.

Global QOL

Mean baseline global QOL scores for the locally advanced and post-surgery cohorts were 53.21 and 58.33, respectively. Pattern of change in global QOL from baseline is shown in Figure 1. The locally advanced group showed a significant and clinically important improvement in global QOL by the end of induction chemotherapy (12.8%, $p = .008$). Subsequent change scores remained positive, but were no longer significant

and showed a trend of decline. In contrast, the post-surgery cohort showed an initial non-significant decline in global QOL at the end of induction chemotherapy, after which there was a progressive improvement becoming significant and clinically important (15.3%, $p = .03$) by four weeks after (time-point 3). This improvement was maintained at time-point 4, but was no longer significant.

Profile of function and symptom change

Baseline to time-point 1 (end of induction gemcitabine): Subscales explaining the significant 12.8% improvement in global QOL score in the locally advanced group are shown in Figure 2A; pain and pancreatic pain were significantly improved ($p = .001$ and $p = .005$, respectively). While the remaining subscale changes were non-significant, most of the trends indicated improvement. This pattern contrasts with a trend of impaired change scores particularly for worsening nausea and vomiting symptoms for the post-surgical arm (Figure 2B), however none were significant.

Baseline to time-point 2 (end of RT/5FU): As shown in Figure 3A, global QOL and pain scores remained positive, but were no longer significant in the locally advanced group. Significant worsening was observed for social function, appetite, diarrhea and nausea and vomiting (all $p < .04$). In the post-surgery cohort significant worsening continued for nausea and vomiting only ($p = .02$), with sexuality and digestive symptoms showing only worsening trends (Figure 3B). Insomnia was the only scale in which a significant and important improvement was seen ($p = .05$).

Baseline to time-point 3 (four weeks after RT/5FU): Global QOL remained positive, but was non-significant in the locally advanced group. Figure 4A shows that

pain improvement remained significant and clinically important (p = .04) and significant improvements were now found for digestive and hepatic symptoms (p = .049 and p = .02, respectively). Significant worsening was only observed for the financial and satisfaction with health care domains in this group (p = .03 and p = .02). In contrast, the post-surgery patients (Figure 4B) now reported significant improvements in global QOL, insomnia and emotional and role function all of which were also clinically significant (all p < .03). A trend for worsening bowel habit, satisfaction with health care and sexuality were reported by this cohort.

Baseline to time-point 4 (end of treatment): The profile of changes differed markedly between groups (Figure 5). Of note was the significant worsening in physical function (p = .03) in the locally advanced group, although hepatic symptoms were significantly better at this assessment (p = .03). In contrast, the post-surgery group showed a general trend of improvement, which was significant and clinically important for role and emotional function, as well as insomnia, appetite, digestive symptoms and pancreatic pain (all p < .024).

DISCUSSION

QOL measurement is widely regarded as an essential endpoint in clinical trials and was particularly important in this Phase II study, because the OS of patients with pancreatic cancer remains quite poor (1). The specific role of chemo-radiotherapy for pancreatic cancer in both the definitive and postoperative settings is controversial with concerns about its potential impact on QOL limiting its use. This study provides a comprehensive analysis of the QOL of patients with locally advanced and resectable pancreatic cancer who received induction gemcitabine chemotherapy followed by RT/5FU and consolidation gemcitabine. The main findings of our investigation were that the impact of our six month treatment program did not worsen global QOL compared with baseline and that global QOL varied between the locally advanced and post-operative groups.

The treatment protocol used in our study has previously been found to be safe and effective for patients both in the locally advanced (10) and the post-surgery arm (9) Here we found improved global QOL at each time-point in locally advanced patients and a trend of progressive improvement in global QOL, maximal at treatment end in the post-surgery group. These findings support the work of Crippa et al. (17) who reported that patients who had surgical resection had better QOL at six months than those with locally advanced or metastatic disease.. These subjective patient reported outcomes are also in keeping with our previously reported modest toxicity levels (grade 3 and 4 toxicities in both arms combined were 39.7% and 11.1% of patients, respectively (9)) and support the overall view that the treatment protocol was well tolerated and did not have a negative impact on patients' quality of life.

This study also extends the work of Carter et al. (18) and Heras et al. (19) who also used the EORTC QLQ–C30 questionnaire with pancreatic cancer patients by administering a pancreatic cancer specific questionnaire (QLQ–PAN26) giving an exploratory insight into function and symptom changes that may have affected global QOL. The improvements in local symptoms such as pain and digestive symptoms, common in pancreatic patients, suggests that patients with such symptoms at baseline are most likely to benefit from the addition of RT. Our report emphasizes that attention to in-depth patient reported outcomes when evaluating novel systemic therapies may result in better identification of patients most likely to derive major benefit. We believe that simply highlighting small differences in progression-free survival or OS in the absence of adjustment for QOL effects may lead to inappropriate treatment recommendations.

Similarly, when discussing the role of adjuvant RT with patients a clear explanation of the temporary effect on significant aspects of QOL may allow for a more informed decision making process. Thorough investigation of the many aspects comprising QOL in studies like ours forms the basis for carefully selecting targeted interventions that will likely improve tolerance of therapy.

For example, previous studies have highlighted that patients with pancreas cancer experience high levels of fatigue which is significantly associated with impaired overall health-related QOL (20) and our findings support this observation. Worsening fatigue was reported by patients in both treatment cohorts, with locally advanced patients showing little recovery in contrast to the post-surgery patients who reported improved fatigue and significant improvement in insomnia after RT/5FU. Improved

fatigue and insomnia in the post-surgery cohort could be related to smaller radiation field size and more favorable tumor characteristics (lower stage and resected disease). We suggest that regular fatigue screening throughout treatment, particularly following high dose adjuvant RT could usefully identify patients who may benefit from targeted fatigue interventions.

The following limitations warrant discussion. First, the proportion of female participants was higher in both cohorts and may have introduced bias. Care was taken to ensure all patients completed both questionnaires at each follow-up, but given the short OS associated with pancreatic cancer the number of returned forms declined over time. In the locally advanced group 85% of patients relapsed systemically, by time-point 3 (four weeks after RT/5FU) 31% patients had progressed and 66% patients progressed by time-point four (treatment end). The steady but non-significant decline in incremental improvement over baseline may reflect subclinical disease progression or some delayed impact of treatment. Importantly, it cannot identify any adverse impact of treatment on those who progress rapidly. As a result our data should be interpreted with caution; however, for those without overt disease progression we find no suggestion of an adverse effect of this approach.

Older two-dimensional RT techniques can adversely affect outcomes for combined modality treatment (4, 5). We have previously established the safety of modern 3DCRT techniques and now report that a six-month course of combined modality therapy employing a carefully directed 3DCRT technique is tolerable based on subjective patient reported outcome measures and that global QOL is not adversely affected. The absence of a negative impact on overall QOL encourages support for the

ongoing Phase III GERCOR LAP-07 trial, comparing chemotherapy to chemotherapy followed by 3D chemo-radiation, which will definitively test the impact of radiation in locally advanced pancreatic cancer.

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FIGURE LEGENDS

Figure 1. Change in global QOL scores over time compared to baseline QOL. Abbreviations: LA – Locally advanced; PS – Post-surgery; *significant difference $p < .05$.

Figure 2. Changes in QOL scores between time-point 1 and baseline. A – Locally advanced. B – Post-surgery. Abbreviations: PF - physical functioning; RF - role functioning; EF - emotional functioning; CF - cognitive functioning; SF - social functioning; GQOL - global quality of life; FA - fatigue; NV - nausea/vomiting; PA - pain; DY - dyspnea; IN - insomnia; AP - appetite loss; CO - constipation; DI - diarrhea; FI - financial problems; PanPA - pancreatic pain; DigSY - digestive symptoms; AltBH - altered bowel habit; HEP - hepatic symptoms; BodIM - body image; SatHC - satisfaction with health care; SEX - sexuality; *significant difference $p < .05$. Data values shown for global QOL and fatigue subscales.

Figure 3. Changes in QOL scores between time-point 2 and baseline. A – Locally advanced. B – Post-surgery. Abbreviations as per Figure 2.

Figure 4. Changes in quality of life scores between time-point 3 and baseline. A – Locally advanced. B – Post-surgery. Abbreviations as per Figure 2.

Figure 5. Changes in quality of life scores between time-point 4 and baseline. A – Locally advanced. B – Post-surgery. Abbreviations as per Figure 2.