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ORIGINAL REPORT

Pain and Emotional Well-Being Outcomes in Southwest Oncology Group–Directed Intergroup Trial S0205: A Phase III Study Comparing Gemcitabine Plus Cetuximab Versus Gemcitabine As First-Line Therapy in Patients With Advanced Pancreas Cancer

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See accompanying articles on pages 3605 and 3617

A B S T R A C T

Purpose
S0205 was a randomized clinical trial that compared the therapeutic impact of gemcitabine versus gemcitabine plus cetuximab. Study results for patient-reported health-related quality of life (HRQL) outcomes are reported.

Patients and Methods
Patients completed the Brief Pain Inventory and a measure of emotional well-being (each measured on a 0 to 10 scale) at baseline and at weeks 5, 9, 13, and 17 postrandom assignment. Worst pain status was classified as palliated (worst pain scores < 5 maintained for 2 consecutive cycles) or not palliated (remaining patients) and tested with a χ^2 test. Change in emotional well-being and worst pain (exploratory analysis) were assessed over 17 weeks using generalized estimating equations with inverse probability of censoring weights.

Results
Seven hundred twenty of 766 enrolled patients contributed baseline HRQL data. The two treatment arms did not differ statistically in the percentage of patients with successful worst pain palliation. Longitudinal analyses showed significantly improved emotional well-being for patients on both arms by weeks 13 and 17 ($P < .01$ and $P < .001$). An exploratory longitudinal analysis of worst pain showed significant decreases at all time points for both arms ($P < .01$ and $P < .001$). Significant treatment arm differences for either worst pain or emotional well-being were not observed at any of the assessment times.

Conclusion
We observed palliated pain and improved well-being for patients on this trial. However, these improvements were similar in both treatment arms, suggesting that the addition of cetuximab did not contribute to improvement in these HRQL outcomes.

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INTRODUCTION

When treatments are compared in advanced-stage disease, particularly for cancers with poor prognosis (eg, pancreatic cancer), it is of interest to study whether the treatments confer palliation. Should one regimen show therapeutic benefit (eg, improved survival), it is of interest to assess whether this treatment also confers benefit or decrement in patient health–related quality of life (HRQL).[1] Conversely, a regimen that might not contribute therapeutic impact may still be beneficial in palliation of symptoms and improved HRQL.

Pain is a common symptom reported by patients with pancreatic cancer, particularly those with advanced-stage disease.[2,3] Fasanella et al[3] also suggested that both pain and HRQL should be measured prospectively in patients with pancreatic cancer. Depressive symptoms have also been reported for patients with pancreatic cancer.[4-7] Jacobson[1] suggested that addressing pain and psychological symptoms was important not only for providing

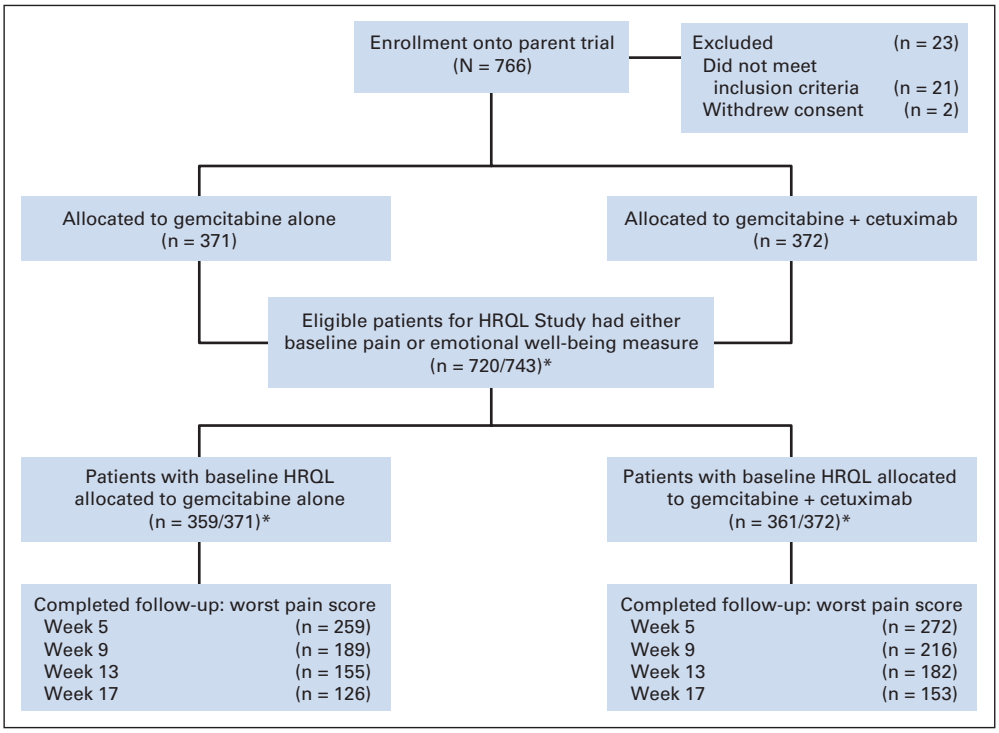

Fig 1. CONSORT diagram for S0205 clinical and health-related quality of life (HRQL) samples. (*) Denominators give total number of eligible patients; numerators give number of eligible patients with baseline HRQL data.

comfort for patients but also for promoting treatment adherence and understanding the biology of the disease.

Because the combination arm (gemcitabine plus cetuximab [GC]) compared with gemcitabine alone was expected to improve overall survival by 6 to 8 months and improve tumor response (20% *v* 10%), we hypothesized that the combination arm would result in improved pain control and better emotional well-being. Therefore, we measured HRQL and identified worst pain and emotional well-being as prespecified patient-reported outcomes for a phase III study in advanced/metastatic pancreatic cancer comparing two gemcitabine-based treatment regimens.

PATIENTS AND METHODS

Patients

Patients were required to have a histologic or cytologic diagnosis of pancreatic adenocarcinoma with locally advanced or distant metastatic disease; patients with endocrine tumors or lymphoma of the pancreas and those with brain metastases were ineligible for S0205. The trial compared the impact of gemcitabine versus GC on clinical and patient-reported outcomes. Additional eligibility criteria and details regarding treatment administration and clinical outcomes are described by Philip et al.[8]

All enrolled patients signed informed consent, and the protocol was approved by institutional review boards of each participating institution in the Southwest Oncology Group (SWOG) and at sites associated with other cooperative groups or the Clinical Trials Support Unit. The Eastern Cooperative Oncology Group, Cancer and Leukemia Group B, North Central Cancer Treatment Group, and the National Cancer Institute of Canada Clinical Trials Group participated through the Clinical Trials Support Unit.

HRQL Assessment

HRQL measures were secondary end points in this trial. Patients completed assessments of pain, pain medication use, and HRQL at the time of registration to the trial (week 0), and at weeks 5, 9, 13, and 17 (Fig 1).

Pain

Patient-reported pain was assessed with the Brief Pain Inventory (BPI).[9-14] The BPI has the following items: yes/no question about pain today; four pain rating questions (ie, worst pain, least pain, average pain, and current pain); pain medications and pain relief; seven items addressing effect of pain on functioning (eg, general activity, mood). The four pain items and seven functioning items have a 0 to 10 response scale, with higher scores reflecting more pain or more interference with functioning. Psychometric properties of this scale have been documented.[9,10,12] Substantial or moderate to severe pain has been defined as a score of 5 or higher for the worst pain item.[13,14] A 2-point difference on a 0 to 10 numeric rating scale has also been documented as clinically significant and applied to the BPI.[15]

Pain palliation (a responder) in this trial was defined as a worst pain score of 4 or lower on a scale of 0 to 10, maintained for two consecutive cycles; scores of ≤ 4 represent mild to moderate pain.[14] A patient whose pain was classified as stable (baseline worst pain score of < 5 maintained for one additional cycle or was < 5 at two nonconsecutive cycles during the 17 weeks) was not counted as a pain responder.

Emotional Well-Being and General HRQL

Because patients with pancreatic cancer are known to report depression and compromised emotional well-being, we included a measure of emotional well-being along with the pain measure.[16] HRQL was assessed with an eight-item linear analog self-assessment (LASA) questionnaire based on LASA scales used in studies conducted by Mayo Clinic investigators (B.K. Donato, personal communication, May 2002). Mayo Clinic response options for the LASA items that included the S0205 emotional well-being item were of three types: five divisions on a horizontal line ranging from very bad to very good,[17] a traditional 0 to 100 LASA response scale[18]; a 0 to 10 response scale has also been validated in 2007.[19] The Locke et al[19] response scale used the same 0 to 10 anchor labels included in our LASA assessment (0 [as bad as it can be]) to 10 [as good as it can be]). SWOG's TeleForm system for forms could not accommodate the traditional 0 to 100 LASA format. In addition, 0 to 10 response scales have been shown to be as responsive as 0 to 100 scales.[20-22] Nunnally[23] noted that not much was gained in the amount of discrimination beyond 11 levels for single-item measures. This report focuses only on the prespecified emotional well-being item.

In S0205, a change of at least 10% (1 or more points on the 0 to 10 scale) for the emotional well-being item was considered clinically significant for this continuous outcome.[24] The 10% change criterion was used to interpret the amount of change in emotional well-being observed for each treatment arm, not to create a responder variable as for worst pain.

Analgesic Use

The patient medication log captured analgesic use. Patients reported their use of pain medication for the 24-hour period before a clinic visit each cycle. The pain medication log was based on a measure used in a previous SWOG trial and modified for ease of data entry to include the following information: an analgesic code (ie, no analgesic, non-narcotic agent, weak opioid, strong opioid), medication delivery type (ie, pill, liquid, pump, or patch), the dose, and the number of doses taken.[25,26]

Statistical Considerations

HRQL measures were secondary outcomes in the clinical trial. Two of these secondary outcomes were prespecified as primary HRQL outcomes: pain palliation (worst pain) and change in emotional well-being; we expected more improvement in worst pain and emotional well-being for the GC arm versus the gemcitabine arm. However, it is often the case that additional therapy (in this case a recombinant monoclonal antibody added to a chemotherapy regimen) will confer more adverse effects and toxicities and not improve quality of life. For this analysis, criteria were specified above to identify clinically significant change and to address potentially positive and negative effects of adding a second agent to a regimen.

Primary Pain Palliation Outcome. The statistical comparison of pain palliation (responder *v* nonresponder) was conducted using the χ^2 test.

Longitudinal Analyses for Continuous Outcomes: Emotional Well-Being (primary) and Pain (exploratory): Nonrandom Missing Data. HRQL measures were obtained for each patient at multiple times (baseline, weeks 5, 9, 13, 17) during the conduct of the study. In order to assess patterns of patient response over this study time, we applied statistical analyses appropriate to the longitudinal nature of these data. Moreover, the number of responses was not identical for each patient, with missing data most often due to disease progression and death. This so-called nonrandom missing data must also be accounted for in any analyses.

We examined plots of mean scores for patients who submitted different numbers of forms to see if the trajectories of continuous measures (ie, 0 to 10 scores) of emotional well-being and worst pain (ie, exploratory analysis) differed for these cohorts.[27-29] Trajectories suggesting more random missing data would indicate that standard generalized estimating equations, which assume that data are missing completely at random, were appropriate.[30]

However, examination of the cohort plots suggested nonrandom missing data (data not shown) supporting the need for an analysis that does not make this assumption. The Kurland and Heagerty strategy[31] conditions on survival status, allowing for valid inference in the presence of significant missing data due to death and when survival is related to the longitudinal HRQL end point. Inverse probability of censoring weights (IPCW) were applied to adjust for any nonrandom missingness. This approach proceeds by first estimating the probability that data were missing for a particular patient at a particular assessment time and then using these fitted probabilities as weights in a generalized estimating equations regression analysis of the outcomes listed above.[32] In this manner, the pattern of missing data is explicitly incorporated into the longitudinal analysis of quality of life outcomes. The following predictors were included in missingness models: baseline HRQL measures, age, metastatic disease, prior pancreatectomy, and Zubrod performance status. In addition to the IPCW analysis, we fit pattern mixture models of the longitudinal data to assess consistency of results between these two approaches.[33,34] The two approaches did not differ substantially. We focus here on the IPCW analysis.

Table 1. Description of the 720 Eligible Patients With Either a Baseline Worst Pain Score or a Baseline Emotional Well-Being Score

Characteristic	%	
	Gemcitabine (n = 359)	Gemcitabine + Cetuximab (n = 361)
Median age, years	65	64
Range	33-91	30-87
Race		
White	87	88
Black	9	7
Other	4	5
Sex		
Male	55	52
Female	45	48
Performance status		
0-1	87	87
2	13	13
Prior chemotherapy	4	6
Prior pancreatectomy	10	9
Metastatic disease	78	79

RESULTS

Patient Characteristics

Between January 2004 and April 2006, a total of 766 patients were enrolled on the trial, with 743 eligible for the primary analysis. The baseline characteristics of the 720 eligible patients with baseline HRQL data are presented in Table 1. Primary trial participants who did and did not report baseline HRQL data did not differ statistically for any of these same characteristics. Table 2 presents the maximum analgesic code level (ie, none, non-narcotic, weak opioid, strong opioid) reported by patients for the 24-hour period before each of the clinic visits involving required HRQL assessments. Approximately 70% to 80% of patients in both arms required weak or strong opioid agents throughout the 17-week assessment period.

HRQL Submission Rates

Percentages of submitted forms with a worst pain score were 96, 85, 83, 88, and 85 for weeks 1, 5, 9, 13, and 17, respectively; submission rates for the emotional well-being item were 96, 87, 84, 88, and 87 for the five scheduled assessments. The GC arm had better submission rates than the gemcitabine alone arm did, consistent with the longer time to treatment failure on the combination arm reported by Philip et al.[8] The most common reasons for missing BPI forms were institutional error (eg, forgetting to administer the questionnaire) and patient illness; a similar distribution of reasons was observed for the LASA form. However, submission rates for forms do not provide a complete picture of the amount of missing data since they are based on patients being alive and on study long enough to reach a particular assessment point. Therefore, we provide numbers of patients available for descriptive analyses below.

Descriptive Results

Means and standard deviations for the worst pain item on the BPI and for the LASA emotional well-being item are presented for

Table 2. Maximum Analgesic Code by Assessment Time and Treatment Arm

Assessment Time and Maximum Analgesic Code	Gemcitabine		Gemcitabine + Cetuximab	
	No.	%	No.	%
Baseline (n = 411)				
No. of patients	206		205	
No analgesic	5	2	9	4
Non-narcotic	40	19	33	16
Weak opioid	69	34	77	38
Strong opioid	92	45	86	42
Week 5 (n = 282)				
No. of patients	141		141	
No analgesic	6	4	7	5
Non-narcotic	23	17	18	13
Weak opioid	44	31	50	35
Strong opioid	68	48	66	47
Week 13 (n = 227)				
No. of patients	104		123	
No analgesic	3	3	5	4
Non-narcotic	13	13	24	19
Weak opioid	40	38	34	28
Strong opioid	48	46	60	49
Week 17 (n = 187)				
No. of patients	85		102	
No analgesic	3	4	8	8
Non-narcotic	15	18	17	17
Weak opioid	30	35	28	27
Strong opioid	37	43	49	48

each assessment time in Table 3. Both arms began the trial with similar levels of worst pain and emotional well-being. By week 13, there was a substantial number of missing HRQL forms. In both treatment arms after baseline, mean worst pain scores were lower and mean emotional well-being scores were higher at later time points. In the gemcitabine arm, both mean worst pain and emotional well-being appear to improve over the entire observation time. However, the initial improvement in both scores achieved in the GC arm by the first assessment time failed to show improvement for later time periods.

Worst Pain Score

The primary HRQL end point of successful worst pain palliation (a secondary outcome in the trial) was met in 159 (45%) of 357 patients on the GC arm and in 136 (38%) of 355 patients on the gemcitabine arm but this difference was not statistically significant ($P = .09$).

An exploratory, longitudinal analysis was also conducted with the worst pain score. Table 4 presents mean estimates of the change since baseline in worst pain score from this analysis. At all assessment times from week 5 to week 17, patients on both arms had statistically significant ($P < .001$) decreases in worst pain scores from baseline. At week 5, the average improvement over baseline among patients receiving gemcitabine alone and GC was 1.0 and 1.3 worst pain points, respectively. At week 17, the average decline from baseline in worst pain was 3.1 and 2.8 points on gemcitabine alone and GC, respectively. These improvements are also clinically significant for both arms as defined in the methods section (at least a 2-point reduction in worst pain from week 9 on). At none of the assessment times was there a significant difference between the arms in improvement in worst pain ($P > .05$).

Emotional Well-Being

Table 4 also presents mean estimates of the change since baseline in emotional well-being from the longitudinal analysis. On neither treatment arm did emotional well-being change significantly from baseline to week 5 or 9 ($P > .05$). At week 13, the average increase from baseline in emotional well-being was 1.0 and 0.6 points on gemcitabine alone and GC, respectively (both $P < .01$). At week 17, the average increase on gemcitabine alone and GC was 2.0 and 1.2 points, respectively (both $P < .001$). The improvement in emotional well-being at week 13 was clinically significant by the 10% criterion for the gemcitabine arm and at 17 weeks for both arms. At none of the assessment times was there a significant difference between the arms in improvement in emotional well-being (ie, $P > .05$).

Table 3. Worst Pain and Emotional Well-Being Scores by Assessment Time

Assessment Time	Worst Pain Score*				Emotional Well-Being Score†			
	Gemcitabine		Gemcitabine + Cetuximab		Gemcitabine		Gemcitabine + Cetuximab	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Baseline	4.5	2.9	4.3	3.1	6.5	2.6	6.6	2.6
No. of patients	355‡		357		354		361	
Week 5	2.9	2.7	2.5	2.7	6.7	2.3	7.0	2.3
No. of patients	259		272		262		278	
Week 9	2.7	2.6	2.4	2.6	7.1	2.3	6.9	2.4
No. of patients	189		216		191		220	
Week 13	2.6	2.8	2.9	3.0	7.1	2.5	6.9	2.6
No. of patients	155		182		157		183	
Week 17	2.3	2.6	3.1	3.0	7.5	2.2	7.0	2.2
No. of patients	126		153		130		158	

Abbreviation: SD, standard deviation.
*Higher scores for the worst pain item reflect more pain.
†Higher scores for the emotional well-being item reflect better emotional well-being.
‡No. of patients with data available for each end point at each time.

Table 4. Inverse Probability of Censoring Weights Estimates of Improvement Since Baseline in Worst Pain and Emotional Well-Being Scores by Assessment Time

Assessment Time (by week)	Decrease in Worst Pain Score*				Increase in Emotional Well-Being Score†			
	Gemcitabine		Gemcitabine + Cetuximab		Gemcitabine		Gemcitabine + Cetuximab	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
5	1.0‡	0.2	1.3‡	0.2	−0.3	0.2	0.1	0.1
9	1.4‡	0.2	1.8‡	0.2	0.4	0.2	0.2	0.2
13	2.2‡	0.3	2.1‡	0.3	1.0§	0.3	0.6§	0.2
17	3.1‡	0.4	2.8‡	0.6	2.0‡	0.4	1.2‡	0.3

Abbreviation: SD, standard deviation.
*Higher scores for the worst pain item reflect more pain.
†Higher scores for the emotional well-being item reflect better emotional well-being.
‡$P < .001$.
§$P < .01$.

DISCUSSION

The primary end point for S0205, overall survival, did not differ significantly for the two treatment arms (one-sided P value = .15); disease progression also did not differ significantly by treatment arm (one-sided P value = .10).[8] Similarly, the primary pain outcome, percentage of pain responders (pain palliation), did not differ statistically by treatment arm. In the secondary, longitudinal analysis of worst pain, a statistically and clinically significant decrease (two points) in worst pain was seen on both arms by week 5; pain scores in both arms continued a modest decline over the study period. Longitudinal analyses of emotional well-being also showed improvement over the study period in both arms, although the time to a statistically significant improvement was longer for this outcome (13 weeks). The improvement in emotional well-being reached clinical significance (1 point) on the gemcitabine arm at 13 weeks and for both arms by the final assessment at week 17. Bernhard et al[35] reported similar clinical benefit response and HRQL for gemcitabine alone versus GC for patients with advanced pancreatic cancer. Clinical benefit response involved improvements in different combinations of pain and performance status outcomes. The authors note that their finding of no difference in HRQL for single-agent gemcitabine versus a combination regimen is consistent with other similar treatment regimen comparisons for this patient group.[36-40]

It is important to note that the significant HRQL differences observed in this study can be characterized as clinically significant. For example, average changes in worst pain (3.1-point reduction) and emotional well-being (2.0-point improvement) for patients receiving gemcitabine over the 17-week assessment period are above the benchmarks of 2 and 1 points described above for worse pain and emotional well-being, respectively. Smaller improvements were observed for the GC arm over time.

A potential source of bias was the overall amount of missing HRQL forms over the course of the assessment period, with more missing data in the gemcitabine arm. For example, 35% of patients receiving gemcitabine completed a final BPI form at 17 weeks compared to 43% of patients receiving GC. Therefore, extrapolating change in emotional well-being and worst pain over the full 17-week assessment period should be considered with respect to the missing data, particularly by weeks 13 and 17; this problem tempers our ability to generalize these longer-term effects to future patients. Both arms did, however, report reductions in worst pain by week 5 before substantial attrition. As noted above, such missing data is common in advanced-stage disease trials, leading to a group of remaining patients who can be characterized as healthy survivors. One can hypothesize that we see improvement in emotional well-being because we are observing the patients who are living longer (maybe longer than they expected to live) and their reports reflect this. Nonetheless, we observed pain palliation in both arms and improvements in emotional well-being over time; these improvements can generally be described as clinically relevant.

Another limitation of these results is our inability to report absolute levels of analgesic use due to our collection of pain medications for the previous 24 hours before a clinic visit at scheduled assessments (random assignment and weeks 5, 9, 13, and 17 postrandomization). We did not incorporate daily diaries of medication use in this trial but instead created a summary variable of analgesic consumption that could be provided by the clinical research associate. Analgesic code levels can be compared for the two treatment arms at the four follow-up assessments. Although dose information is incorporated in the selection of one of the four levels of the analgesic code variable (ie, no pain medications, non-narcotics, weak opioids, or strong opioids), actual dose information is not available for analysis.

We conclude that patients treated on both arms of this study reported clinically and statistically significant improvements in worst pain and emotional well-being over the study period, but that no significant treatment differences between these arms in these HRQL outcomes were observed. Thus, there is no evidence to suggest that the addition of cetuximab contributes to improved pain palliation and improved well-being over treatment with gemcitabine alone.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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