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Short Communication

Meta-analyses of chemotherapy for locally advanced and metastatic pancreatic cancer: results of secondary end points analyses

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In advanced pancreatic cancer, level one evidence has established a significant survival advantage with chemotherapy, compared to best supportive care. The treatment-associated toxicity needs to be evaluated. This study examines the secondary outcome measures for chemotherapy in advanced pancreatic cancer using meta-analyses. A systematic review was undertaken employing Cochrane methodology, with search of databases, conference proceedings and trial registers. The secondary end points were progression-free survival (PFS)/time to progression (TTP) (summarised using the hazard ratio (HR)), response rate and toxicity (summarised using relative risk). There was no significant advantage of 5FU combinations vs 5FU alone for TTP (HR = 1.02; 95% CI = 0.85 – 1.23) and toxicity. Progression-free survival (HR 0.78; CI 0.70 – 0.88), TTP (HR = 0.85; 95% CI = 0.72 – 0.99) and overall response rate (RR = 0.56; 95% CI = 0.46 – 0.68) were significantly better for gemcitabine combination chemotherapy, but offset by the greater grade 3/4 toxicity thrombocytopenia (RR = 1.94; 95% CI = 1.32 – 2.84), leucopenia (RR = 1.46; 95% CI = 1.15 – 1.86), neutropenia (RR = 1.48; 95% CI = 1.07 – 2.05), nausea (RR = 1.77; 95% CI = 1.37 – 2.29), vomiting (RR = 1.64; 95% CI = 1.24 – 2.16) and diarrhoea (RR = 2.73; 95% CI = 1.87 – 3.98). There is no significant advantage on secondary end point analyses for administering 5FU in combination over 5FU alone. There is improved PFS/TTP and response rate, with gemcitabine-based combinations, although this comes with greater toxicity.

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Advanced pancreatic cancer has a poor prognosis, with a median survival of 2-6 months for metastatic disease and 6-11 months for locally advanced disease (Cancer Research, 2006). Chemotherapy with fluoropyrimidines, gemcitabine, either alone or in combination with other agents (Rocha Lima and Flores, 2006), and chemoradiation are all used in the palliative setting (Mancuso et al, 2006). Overall survival meta-analyses, using relative risk (Yip et al, 2006) or the hazard ratio (HR) (Fung et al, 2003; Sultana et al, 2007), have established a role for chemotherapy over best supportive care. Questions have arisen as to the cost at which this survival advantage is gained, in particular, the toxicity profile. Following from our previous survival meta-analysis (Sultana et al, 2007), we present the results of the secondary outcome measures meta-analysis.

There has only been one fully published meta-analysis evaluating secondary outcome measures, with no pooling of the results of these end points (Yip *et al*, 2006). Other published reports have

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assessed this only for the comparison of gemcitabine combinations vs gemcitabine. (Liang, 2005; Milella et al, 2006; Heinemann et al, 2006a; Xie et al, 2006a, b; Bria et al, 2007; Heinemann et al, 2007). To fully evaluate the risks vs the benefits of treatment, a comprehensive evaluation including assessment of several composite end points is required.

METHODS

Detailed description of the methodology of the systematic review has already been described (Sultana et al, 2007).

The secondary outcome measures evaluated were progressionfree survival (PFS – time from randomisation to progression or death) or time to progression (TTP – time from randomisation to disease progression), overall response rate (ORR – number of partial and complete responses) and toxicity (as published by the trialists, was recorded, with the most frequently reported events analysed).

Individual trial level time to event data (PFS/TTP) were summarised by the log HR and its variance was approximated using previously reported methods (Parmar *et al*, 1998; Williamson *et al*, 2002). Trial level log HRs and their variances were pooled using an inverse variance, weighted average and results presented as a HR and 95% confidence interval.

Clinical Studies

Dichotomous data (ORR and toxicity) were summarised using relative risks and 95% confidence intervals and pooled using the Mantel–Haenszel method for combining trials (Deeks *et al*, 2001). Heterogeneity was assessed by visual inspection of the Forrest plot, the Cochran's χ^2 test (using a 10% significance level, in view of the low power of tests for heterogeneity (Paul and Donner, 1992)) and interpretation of the I² statistic (percentage of variation due to heterogeneity with higher values indicating a greater degree of heterogeneity) (Deeks *et al*, 2004). A fixed effect approach was adopted unless there was evidence of significant unexplained heterogeneity in which case a random effects approach was used.

RESULTS

Results are presented for the comparisons with adequate data to assess the secondary outcome measures.

5FU vs 5FU combination chemotherapy

There were five studies (Supplementary Table 1) (Kovach *et al*, 1974; Cullinan *et al*, 1985, 1990; Ducreux *et al*, 2002; Maisey *et al*, 2002) (n = 700) included in this comparison. A HR of < 1 indicates a survival advantage for 5FU combination chemotherapy.

Two trials assessed TTP (Figure 1) and found no significant advantage for 5FU combinations over 5FU alone (HR = 1.02; 95% CI = 0.85 - 1.23). For PFS, 5FU combination appeared better than 5FU alone (two trials; 416 patients; HR = 0.67; 95% CI = 0.46 -0.98). The ORR (Figure 2) was superior (five trials; 700 patients; RR = 0.43; 95% CI = 0.25 - 0.74) in the 5FU combination arm. Grade 3 or 4 vomiting was significantly greater in the 5FU combination chemotherapy arm (two trials; 320 patients; RR = 3.76; 95% CI = 1.67 - 8.44). There was a higher occurrence of diarrhoea (two trials 406 patients; RR = 1.49; 95% CI = 0.58 -3.84), stomatitis (three trials; 529 patients; RR = 1.29; 95% CI = 0.75 - 2.22) and thrombocytopenia (two trials; 332 patients; RR = 2.15; 95% CI = 0.83 - 5.53) in the combination chemotherapy arm (Figure 3). Data for leucopenia, neutropenia, anaemia and nausea are displayed in Figure 3. There was significant between trial heterogeneity in the PFS analysis, unlike for the TTP and response rate analyses.

Gemcitabine vs 5FU

Two randomised controlled trials involving 197 patients were assessed (Burris *et al*, 1997; Cantore *et al*, 2004), including unpublished individual patient data (Cantore *et al*, 2004). A HR of <1 indicates a survival advantage for gemcitabine. Gemcitabine

resulted in survival advantage on TTP analysis, (HR = 0.46; 95% CI = 0.31 – 0.70), but not for PFS analysis (HR = 0.94; 95% CI = 0.58 – 1.53).

Overall response rate appeared better in the gemcitabine arm; however, the wide confidence interval suggests a benefit for either gemcitabine or 5FU (one trial; 126 patients; RR = 0.14; 95% CI = 0.01 – 2.66). In the Burris trial (Burris *et al*, 1997), haematological toxicity was seen more frequently following gemcitabine therapy (grades 3 and 4 neutropenia in 25% of gemcitabine and 4.9% of 5FU patients; P < 0.001).

Gemcitabine vs gemcitabine-based combination chemotherapy

Nineteen studies involving 4697 patients were included (Supplementary Table 2) (Berlin et al, 2002; Colucci et al, 2002; Wang et al, 2002; Heinemann et al, 2003; Scheithauer et al, 2003; Li and Chao, 2004; Ohkawa, 2004; Rocha Lima et al, 2004; Viret et al, 2004; Cunningham et al, 2005; Di Costanzo et al, 2005; Hermann et al, 2005; Louvet et al, 2005; Oettle et al, 2005; Reiss et al, 2005; Reni et al, 2005; Stathopoulos et al, 2005; Abou-Alfa et al, 2006; Poplin et al, 2006; Heinemann et al, 2006b; Stathopoulos et al, 2006; Herrmann et al, 2007) were based on abstracts and extra data provided by the authors (Hermann et al, 2005; Stathopoulos et al, 2005). A HR of <1 indicates a survival advantage for gemcitabine-based combination chemotherapy.

Progression-free survival (four trials; 864 patients; HR = 0.78; 95% CI = 0.70 - 0.88), TTP (3 trials; 559 patients; HR = 0.85; 95% CI = 0.72 - 0.99) (Figure 4) and ORR (Figure 5) (17 trials; 3577) patients; RR = 0.56; 95% CI = 0.46 - 0.68) were significantly better in the gemcitabine combination chemotherapy arm. Haematological toxicity was greater in the gemcitabine combination chemotherapy arm (Figure 6), including thrombocytopenia (18 trials; 4564 patients; RR = 1.94; 95% CI = 1.32 - 2.84), leucopenia (eight trials; 1606 patients; RR = 1.46; 95% CI = 1.15 - 1.86), neutropenia (15 trials; 3818 patients; RR = 1.48; 95% CI = 1.07 -2.05) and anaemia (15 trials; 3745 patients; RR = 1.14; 95% CI = 0.82 - 1.59). Gastrointestinal side effects (Figure 7) of nausea (nine trials; 3055 patients; RR = 1.77; 95% CI = 1.37 - 2.29), vomiting (10 trials; 3471 patients; RR = 1.64; 95% CI = 1.24-2.16) and diarrhoea (14 trials; 3531 patients; RR = 2.73; 95% CI = 1.87 - 3.98) were significantly increased, with a trend towards increased stomatitis (7 trials; 2007 patients; RR=1.84; 95% CI = 0.86 - 3.92) in the gemcitabine combination chemotherapy arm. There was no significant inter-trial heterogeneity for the end points of PFS, TTP and ORR.

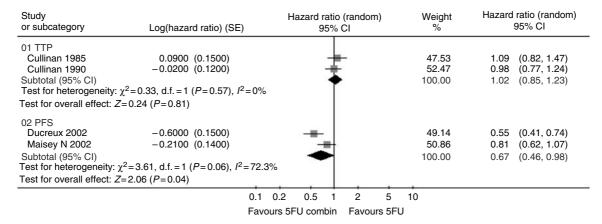
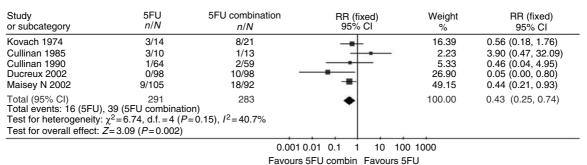


Figure I 5FU single agent vs 5FU-based combination chemotherapy – PFS/TTP analyses.



Legend: *n*=number of responses

N=total number of patients

Figure 2 5FU single agent vs 5FU-based combination chemotherapy – response rate analyses.

Review: Treatment of advanced pancreatic cancer (Version 07; 27 june06)

Comparison: 03 5FU vs 5FU combo

Outcome: 04 Adverse events 5FU combo vs 5FU

5FU combination 5FU alone RR (fixed) Weight RR (fixed) or subcategory n/N n/N 95% CI 95% CI 01 grade3 or 4 thrombocytopenia Cullinan 1990 8/59 4/64 66.28 2.17 (0.69, 6.831) Maisey N 2002 Subtotal (95% CI) 4/102 2/107 33 72 2.10 (0.39, 11.21) 2.15 (0.83, 5.53) 161 Total events: 12 (5FU combination), 6 (5FU alone) Test for heterogeneity: χ^2 =0.00, d.f.=1 (P=0.97), I^2 =0% Test for overall effect: Z=1.58 (P=0.11) 02 grade 3 or 4 leucopenia 20/64 100.00 1.68 (1.09, 2.60) Cullinan 1990 31/59 Subtotal (95% CI) 64 100.00 1.68 (1.09, 2.60) Total events: 31 (5FU combination), 20 (5FU alone) Test for heterogeneity: not applicable Test for overall effect: Z=2.33 (P=0.02) 03 grade 3 or 4 neutropenia Maisey N 2002 3/102 0/107 100.00 7.34 (0.38, 140.36) Subtotal (95% CI) 7.34 (0.38, 140.36) 102 107 100.00 Total events: 3 (5FU combination), 0 (5FU alone) Test for heterogeneity: not applicable Test for overall effect: Z=1.32 (P=0.19) 04 grade 3 or 4 anaemia Maisey N 2002 8/102 9/107 100.00 0.93 (0.37, 2.32) Subtotal (95% CI) 102 107 100.00 0.93 (0.37, 2.32) Total events: 8 (5FU combination), 9 (5FU alone) Test for heterogeneity: not applicable Test for overall effect: Z=0.15 (P=0.88) 05 grade 3 or 4 nausea Cullinan 1990 3/64 100.00 4.70 (1.41, 15.68) 13/59 Subtotal (95% CI) 4.70 (1.41, 15.68) 64 100.00 Total events: 13 (5FU combination), 3 (5FU alone) Test for heterogeneity: not applicable Test for overall effect: Z=2.52 (P=0.01) 06 grade 3 or 4 vomiting Cullinan 1990 9/59 3/64 42.22 3.25 (0.93, 11.45) Ducreux 2002 16/97 4/100 57.78 4.12 (1.43, 11.90) Subtotal (95% CI) 156 164 100.00 3.76 (1.67, 8.44) Total events: 25 (5FU combination), 7 (5FU alone) Test for heterogeneity: $\chi^2 = 0.08$, d.f. = 1 (P = 0.78), $I^2 = 0\%$ Test for overall effect: Z=3.20 (P=0.001) 07 grade 3 or 4 diarrhoea Ducreux 2002 5/97 2/100 28.75 2.58 (0.51, 12.97) 1.05 (0.31, 3.52) 1.49 (0.58, 3.84) Maisey N 2002 5/102 5/107 71.25 Subtotal (95% CI) 199 207 100.00 Total events: 10 (5FU combination), 7 (5FU alone) Test for heterogeneity: $\chi^2 = 0.76$, d.f. = 1 (P = 0.38), $I^2 = 0\%$ Test for overall effect: Z=0.80 (P=0.41) 08 grade 3 or 4 stomatitis Cullinan 1990 9/64 0.36 (0.10, 1.27) 3/59 40.41 Ducreux 2002 13/97 5/100 23.04 2.68 (0.99, 7.23) Maisey N 2002 11/102 8/107 36.55 1.44 (0.60, 3.44) Subtotal (95% CI) 258 271 100.00 1.29 (0.75, 2.22) Total events: 27 (5FU combination), 22 (5FU alone) Test for heterogeneity: χ^2 =6.07, d.f.=2 (P=0.05), I^2 =67.1% Test for overall effect: Z=0.92 (P=0.36) 0.001 0.01 0.1 1 10 100 1000

Favours 5FU combin Favours 5FU

Legend: *n*=number of toxicity events *N*= total number of patients

Figure 3 5FU single agent vs 5FU-based combination chemotherapy – toxicity analyses.

Review: Treatment of advanced pancreatic cancer

Comparison: 04 Gem vs Gem combo

Outcome: 04 TTP/PFS gemcitabine combination *vs* gemcitabine

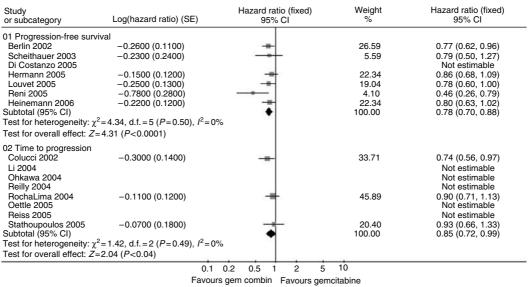


Figure 4 Results for gemcitabine vs gemcitabine-based combination chemotherapy – TTP/PFS.

Study or subcategory	Gemcitabine n/N	Gem combination n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI
Berlin 2002 Colucci 2002 Wang 2002 Scheithauer 2003 Li 2004 Abou-Alfa 2006 Ohkawa 2004 RochaLima 2004 Viret F 2004 Cunningham D 2005 Di Costanzo 2005 Hermann 2005 Louvet 2005 Oettle 2005 Reiss 2005 Reiss 2005 Stathoupoulos 2005	9/162 5/48 1/16 6/42 3/25 11/174 3/9 8/180 2/41 19/266 4/48 12/152 27/156 20/282 0/1 4/47 4/50	11/160 14/45 2/18 7/41 2/21 14/175 0/10 29/180 3/42 38/267 5/43 15/148 42/157 42/283 0/1 20/52 5/42	*	4.26 5.57 0.73 2.73 0.84 5.38 0.18 11.17 1.14 14.61 2.03 5.85 16.13 16.15	0.81 (0.34, 1.90) 0.33 (0.13, 0.85) 0.56 (0.06, 5.63) 0.84 (0.31, 2.28) 1.26 (0.23, 6.85) 0.79 (0.37, 1.69) 7.70 (0.45, 131.36) 0.28 (0.13, 0.59) 0.68 (0.12, 3.88) 0.50 (0.30, 0.85) 0.72 (0.21, 2.50) 0.78 (0.38, 1.61) 0.65 (0.42, 0.99) 0.48 (0.29, 0.79) Not estimable 0.22 (0.08, 0.60) 0.67 (0.19, 2.34)
Heinemann 2006 Poplin 2006	8/97 0/1	10/98 0/1	+	3.83	0.81 (0.33, 1.96) Not estimable
Total (95% CI) Total events: 146 (gemcitt Test for heterogeneity: χ^2 Test for overall effect: Z =	= 16.84, d.f. = 16 (<i>P</i> =0		•	100.00	0.56 (0.46, 0.68)
			0.001 0.01 0.1 1 10 1 Favours gem combin Favours	00 1000 gem	

Figure 5 Results for gemcitabine vs gemcitabine-based combination chemotherapy – response rate.

Examination of the funnel plots revealed evidence of bias, possibly publication bias, but this is difficult to interpret in view of the small number of studies within each comparison.

Legend: *n*=number of responses

N=total number of patients

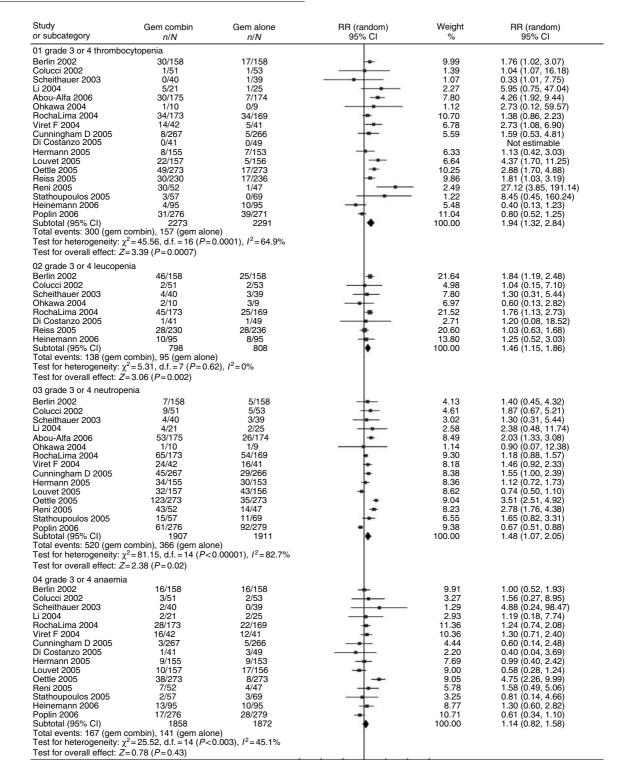
DISCUSSION

5FU combinations did not prolong TTP over 5FU alone, despite significantly better response rate with the former. The study of Yip *et al* (2006) assessed the parameters described in our analyses, but did not pool the results unlike our approach. In the two trials that had assessed PFS, the overall summary estimate favoured 5FU combination chemotherapy, but there was significant inter-trial

heterogeneity. This may be due to the differences in dosing. The dose of 5FU administered was lower in the Maisey *et al* (2002) study (300 mg m $^{-2}$ day $^{-1}$ in both arms) compared to the Ducreux *et al* (2002) study (500 mg m $^{-2}$ day $^{-1}$ used in the single-agent arm and 1000 mg m $^{-2}$ used in the combination arm).

As overall survival is a better indicator of efficacy than response rate (Maisey *et al*, 2002), the evidence from these end points, interpreted alongside the overall survival result (Sultana *et al*, 2007), do not support the use of 5FU combinations over 5FU single agent.

Meta-analyses of the secondary end points were not possible in the gemcitabine νs 5FU comparison, as these results were only available for one randomised trial.



0.001 0.01 0.1

Favours gem combin Favours gem alone

Figure 6 Results for gemcitabine vs gemcitabine-based combination chemotherapy - haematological toxicity.

Previous meta-analyses of secondary end points evaluating gemcitabine-based combinations vs gemcitabine employed differing survival analyses methodology (Liang, 2005; Heinemann et al, 2006a; Milella et al, 2006; Xie et al, 2006a). In contrast to these reports, our survival analyses were conducted using the HR, which is the ideal measure for time-to-event analyses, as it accounts for

Legend: *n*=number of toxicity events *N*=total number of patients

both censoring of data and the time it takes for the event (such as death or progression) to occur (Parmar et al, 1998).

For gemcitabine-based chemotherapy vs gemcitabine alone, our findings of improved PFS/TTP are in agreement with the metaanalyses of Xie et al (2006b). Better ORR with the combination regimens was in keeping with the studies of Xie et al and Milella

tudy r subcategory	Gem combin n/N	Gem alone n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
5 grade 3 or 4 nausea					
erlin 2002	7/158	5/158		5.90	1.40 (0.45, 4.32)
ochaLima 2004	29/173	17/169	_	20.29	1.67 (0.95, 2.92)
iret F 2004	6/42	2/41		2.39	2.93 (0.63, 13.68)
ermann 2005	8/155	5/153		5.94	1.58 (0.53, 4.72)
ouvet 2005	16/157	9/156	7=	10.65	1.77 (0.80, 3.88)
ettle 2005			L-	9.44	1.13 (0.44, 2.87)
	9/273	8/273			
eiss 2005	32/230	17/236	-	19.80	1.93 (1.10, 3.38)
athoupoulos 2005	1/57	2/69		2.13	0.61 (0.06, 6.51)
plin 2006	42/276	20/279		23.47	2.12 (1.28, 3.52)
btotal (95% CI)	1521	1534	♦	100.00	1.77 (1.37, 2.29)
tal events: 150 (gem co st for heterogeneity: χ ² =), <i>I</i> ² =0%			
st for overall effect: $Z=4$					
grade 3 or 4 vomiting	11/150	10/150		17.00	0.05 (0.00 1.00)
erlin 2002	11/158	13/158	-	17.32	0.85 (0.39, 1.83)
ou-Alfa 2006	19/175	9/174	-	12.02	2.10 (0.98, 4.51)
chaLima 2004	24/173	14/169	 = -	18.87	1.67 (0.90, 3.13)
et F 2004	3/42	1/41		1.35	2.93 (0.32, 27.02)
inningham D 2005	3/267	5/266		6.67	0.60 (0.14, 2.48)
ermann 2005	6/155	3/153	+	4.02	1.97 (0.50, 7.75)
uvet 2005	14/157	5/156	-	6.68	2.78 (1.03, 7.54)
ettle 2005	9/273	10/273	-	13.32	0.90 (0.37, 2.18)
athoupoulos 2005	1/57	1/69		1.21	1.21 (0.08, 18.93)
plin 2006	33/276	14/279	-	18.55	2.38 (1.30, 4.35)
btotal (95% CI)	1733	1738	•	100.00	1.64 (1.24, 2.16)
tal events: 123 (gem co	mbin), 75 (gem alone)		I.		- (, -,
est for heterogeneity: χ^2 =	9.86. d.f. = 9 (P=0.36)	. /2=8.8%			
est for overall effect: $Z=3$,			
001.101.0101.411.011.0011.2			I		
7 grade 3 or 4 diarrhoea					
7 grade 3 or 4 diarrhoea erlin 2002	16/158	6/158	-	16.76	2.76 (1.07, 6.64)
grade 3 or 4 diarrhoea	16/158 2/51	6/158 0/53	-	16.76 1.37	2.76 (1.07, 6.64) 5.19 (0.26, 105.59)
grade 3 or 4 diarrhoea erlin 2002			-		
grade 3 or 4 diarrhoea erlin 2002 blucci 2002 eheithauer 2003	2/51	0/53	-	1.37	5.19 (0.26, 105.59)
grade 3 or 4 diarrhoea erlin 2002 olucci 2002 heithauer 2003 okawa 2004	2/51 2/40	0/53 0/39	-	1.37 1.41	5.19 (0.26, 105.59) 4.88 (0.24, 98.47)
grade 3 or 4 diarrhoea erlin 2002 olucci 2002 theithauer 2003 okawa 2004 ochaLima 2004	2/51 2/40 1/10	0/53 0/39 0/9	-	1.37 1.41 1.46 8.48	5.19 (0.26, 105.59) 4.88 (0.24, 98.47) 2.73 (0.12, 59.57) 10.42 (3.25, 33.38)
grade 3 or 4 diarrhoea Irlin 2002 Ilucci 2002 Iheithauer 2003 Ikawa 2004 Inningham D 2005	2/51 2/40 1/10 32/173 3/267	0/53 0/39 0/9 3/169 3/266		1.37 1.41 1.46	5.19 (0.26, 105.59) 4.88 (0.24, 98.47) 2.73 (0.12, 59.57) 10.42 (3.25, 33.38) 1.00 (0.20, 4.89)
grade 3 or 4 diarrhoea brlin 2002 blucci 2002 cheithauer 2003 hkawa 2004 bochaLima 2004 unningham D 2005 Costanzo 2005	2/51 2/40 1/10 32/173 3/267 0/41	0/53 0/39 0/9 3/169 3/266 0/49		1.37 1.41 1.46 8.48 8.39	5.19 (0.26, 105.59) 4.88 (0.24, 98.47) 2.73 (0.12, 59.57) 10.42 (3.25, 33.38) 1.00 (0.20, 4.89) Not estimable
grade 3 or 4 diarrhoea Irlin 2002 Jucci 2002 heithauer 2003 Iskawa 2004 IchaLima 2004 Inningham D 2005 Costanzo 2005 Ermann 2005	2/51 2/40 1/10 32/173 3/267 0/41 8/155	0/53 0/39 0/9 3/169 3/266 0/49 3/153		1.37 1.41 1.46 8.48 8.39 8.43	5.19 (0.26, 105.59) 4.88 (0.24, 98.47) 2.73 (0.12, 59.57) 10.42 (3.25, 33.38) 1.00 (0.20, 4.89) Not estimable 2.63 (0.71, 9.74)
grade 3 or 4 diarrhoea rlin 2002 lucci 2002 heithauer 2003 skawa 2004 chaLima 2004 inningham D 2005 Costanzo 2005 irmann 2005 uvet 2005	2/51 2/40 1/10 32/173 3/267 0/41 8/155 9/157	0/53 0/39 0/9 3/169 3/266 0/49 3/153 2/156		1.37 1.41 1.46 8.48 8.39 8.43 5.60	5.19 (0.26, 105.59) 4.88 (0.24, 98.47) 2.73 (0.12, 59.57) 10.42 (3.25, 33.38) 1.00 (0.20, 4.89) Not estimable 2.63 (0.71, 9.74) 4.47 (0.98, 20.36)
grade 3 or 4 diarrhoea rlin 2002 lucci 2002 heithauer 2003 Ikawa 2004 chaLima 2004 Inningham D 2005 Costanzo 2005 Irmann 2005 uvet 2005	2/51 2/40 1/10 32/173 3/267 0/41 8/155 9/157 8/273	0/53 0/39 0/9 3/169 3/266 0/49 3/153 2/156 2/273		1.37 1.41 1.46 8.48 8.39 8.43 5.60 5.59	5.19 (0.26, 105.59) 4.88 (0.24, 98.47) 2.73 (0.12, 59.57) 10.42 (3.25, 33.38) 1.00 (0.20, 4.89) Not estimable 2.63 (0.71, 9.74) 4.47 (0.98, 20.36) 4.00 (0.86, 18.67)
grade 3 or 4 diarrhoea rlin 2002 lucci 2002 heithauer 2003 ikawa 2004 ichaLima 2004 inningham D 2005 Costanzo 2005 irmann 2005 uvet 2005 ittle 2005 iss 2005	2/51 2/40 1/10 32/173 3/267 0/41 8/155 9/157 8/273 9/230	0/53 0/39 0/9 3/169 3/266 0/49 3/153 2/156 2/273 9/236		1.37 1.41 1.46 8.48 8.39 8.43 5.60 5.59 24.81	5.19 (0.26, 105.59) 4.88 (0.24, 98.47) 2.73 (0.12, 59.57) 10.42 (3.25, 33.38) 1.00 (0.20, 4.89) Not estimable 2.63 (0.71, 9.74) 4.47 (0.98, 20.36) 4.00 (0.86, 18.67) 1.03 (0.41, 2.54)
grade 3 or 4 diarrhoea rlin 2002 lucci 2002 heithauer 2003 lokawa 2004 chaLima 2004 Inningham D 2005 Costanzo 2005 Irmann 2005 uvet 2005 sittle 2005 inis 2005	2/51 2/40 1/10 32/173 3/267 0/41 8/155 9/157 8/273 9/230 1/52	0/53 0/39 0/9 3/169 3/266 0/49 3/153 2/156 2/273 9/236 0/47		1.37 1.41 1.46 8.48 8.39 8.43 5.60 5.59 24.81 1.47	5.19 (0.26, 105.59) 4.88 (0.24, 98.47) 2.73 (0.12, 59.57) 10.42 (3.25, 33.38) 1.00 (0.20, 4.89) Not estimable 2.63 (0.71, 9.74) 4.47 (0.98, 20.36) 4.00 (0.86, 18.67) 1.03 (0.41, 2.54) 2.72 (0.11, 65.12)
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grade 3 or 4 diarrhoea urlin 2002 olucci 2002 heithauer 2003 oluca 2004 oluchalima 2004 oluchalima 2005 costanzo 2005 oluca 2005 olu	2/51 2/40 1/10 32/173 3/267 0/41 8/155 9/157 8/273 9/230 1/52 2/57 3/95 1759 abin), 34 (gem alone) =15.72, d.f. =12 (P=0.3 5.22 (P<0.0001)	0/53 0/39 0/9 3/169 3/266 0/49 3/153 2/156 2/273 9/236 0/47 2/69 4/95 1772 36), I ² =23.7% 3/158 0/39 0/266 1/153		1.37 1.41 1.46 8.48 8.39 8.43 5.60 5.59 24.81 1.47 5.05 11.17 100.00	5.19 (0.26, 105.59) 4.88 (0.24, 98.47) 2.73 (0.12, 59.57) 10.42 (3.25, 33.38) 1.00 (0.20, 4.89) Not estimable 2.63 (0.71, 9.74) 4.47 (0.98, 20.36) 4.00 (0.86, 18.67) 1.03 (0.41, 2.54) 2.72 (0.11, 65.12) 1.21 (0.18, 8.33) 0.75 (0.17, 3.26) 2.73 (1.87, 3.98) 0.67 (0.11, 3.94) 2.93 (0.12, 69.74) Not estimable 0.33 (0.01, 8.02)
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Favours gem combin Favours gem alone

Figure 7 Results for gemcitabine vs gemcitabine-based combination chemotherapy – gastrointestinal toxicity.

et al (Xie et al, 2006b), while increased toxicity profile was noted by Xie et al (2006b). The meta-analyses that examined gemcitabine plus a platinum agent vs gemcitabine alone found better PFS/TTP in the combination arm (Xie et al, 2006a; Heinemann et al, 2007), significant improvement in ORR (Heinemann et al, 2007) and greater toxicity (Xie et al, 2006a).

Legend: *n*=number of toxicity events *N*=total number of patients

We have done our utmost to cover most reported end points in the randomised controlled trials. We could not address quality of life due to the different methods used for reporting quality of life. Although we have pooled the response rate and adverse events data across studies to permit a clinically relevant analysis, reporting of these parameters varied. Response rates were reported using clinical parameters, the WHO and RECIST criteria, whereas the CTC, WHO and ECOG scales were used for toxicity data.

To conclude, there is insufficient evidence to suggest a TTP, response rate and toxicity advantage in administering 5FU in combination with other chemotherapy agents over 5FU alone. There is a small but significant TTP/PFS advantage, as well as improved response rate, with gemcitabine-based combinations, and this provides a justification for the use of these agents, despite their greater toxicity. An area for further randomised controlled trials to assess is which gemcitabine-based combination chemotherapy regimens are least toxic, while retaining all the other advantages of the combination approach.

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