

Palliative symptom management in metastatic pancreatic cancer

Prof. dr. C. Verslype
Hepatology – Digestive Oncology
University Hospital Gasthuisberg
Leuven - Belgium

Disclosures

No relevant financial relationships to disclose

Pancreatic cancer: facts

- 4th cause of cancer death
- Median survival: ± 5 months
- 1 yr survival <15%
- 80-90% of patients have metastases or a locally inoperable tumour
 - survival (w/o chemotherapy): 3-4 months
 - rapid progression and poor performance status
 - evaluation of new drugs is difficult (often unmeasurable disease)

Verslype et al. Ann Oncol, 2007

Overview

- Quality of life
- Jaundice
- Pain
- Nutrition and pancreatic enzymes
- Impact of chemotherapy on QoL

Advanced pancreatic cancer and QoL

- Most patients are symptomatic and cannot be cured
 - E.g. study n = 688: weight loss: 56%, pain: 76%*
- Any therapeutical intervention may:
 - Improve QoL or halt the deterioration of QoL
 - Negatively influence QoL

*Van Cutsem et al. JCO, 2004

Measurement of QoL

- Difficult, several instruments, compliance ...
- Conditions:
 - by the patient
 - before any information is given concerning disease evolution
 - before (chemo)therapy administration

Measurement of QOL

- EORTC QLQ-C30 questionnaire:
 - Validated, cancer-specific instrument for prospective clinical studies
 - 5 functional scales (physical, role, cognitive, emotional, social), 3 symptom scales (fatigue, pain, nausea/vomiting), global health status/QOL scale, and 6 separate symptoms (dyspnoea, sleep disturbance, appetite, constipation, diarrhea and financial problems).
- Specific for pancreatic cancers: EORTC QLQ-PAN26

Domains of the EORTC QLQ-PAN26

Emotional and social consequences

- Body image
- Sexuality
- Health care satisfaction
- Burden of treatment
- Planning ahead
- Fear of future

Symptoms/ side effects

- Pain and discomfort
- Diet
- Jaundice
- Altered bowel function
- Flatulence
- Muscle weakness
- Xerostomia
- Taste changes



Obstructive jaundice

- Major impact on QoL: pruritus, abdominal discomfort, nausea, appetite and malabsorption
- Biliary decompression is necessary before applying chemo(radio)therapy
- Limited RCTs: endoscopic treatment with metal stents is recommended
 - Metal stents: less recurrent biliary obstruction than plastic stents
 - 1 study*: QOL scores at 30 and 60 days better in endoscopy group than surgery - Total costs lower in endoscopy group than surgical group*

Ballinger Gut 1994; *Artifon et al., Am J Gastroenterol 2006; Moss et al., 2007 (systematic review, 3 RCT)

Gastric outlet obstruction

- Duodenal stents are indicated for duodenal or gastric obstruction caused by locally advanced or metastatic pancreatic cancer.
 - self-expanding metallic type with diameters of 16–22 mm.
 - minimally invasive and low morbidity

Carr-Locke, Ann Oncol 1999

Peritoneal carcinomatosis: "misery"

- Difficult and understudied item
- Combination of (sub)obstruction and/or ascites
- Symptomatic treatment:
 - Nasogastric tube: poor option
 - Drugs :
 - Anti-emetics
 - Anti-secretory (somatostatin analogs)
 - Anti-inflammatory (steroids)

Pain management

- Advanced pancreatic cancer = pain
- Diagnosis:
 - Type of pain: nociceptive vs. neuropathic
 - "Total pain" (C. Saunders), beyond physical aspects
- Treatment:
 - WHO three-step analgesic ladder
 - Right drug, at the right time, at the right dose is effective in > 90%
 - Neurolytic celiac plexus block in case of severe pain that is unresponsive to other analgesic measures

Yan, Myers. Am J Gastroenterol . 2007 (systematic review of 5 RCTs)

Nutrition

- Weight loss leads to a reduced QoL and wasting frequently accompanies advanced pancreatic cancer*
- Small, frequent, nutrient-dense meals
- Problems of early satiety, pain, nausea and vomiting
- Need for pancreatic enzyme supplementation

*Ravasco et al. 2003

Pancreatic enzyme supplementation

- Pancreatic exocrine failure: significant fat malabsorption.
- Enteric-coated pancreatic enzyme formulations may prevent weight loss and improve QoL.*
- Sufficient dose of enzymatic activity, which should be at least 10% of the normal postprandial output of lipolytic activity (30.000 IU)

*Bruno Gut 1998; 42: 92-96.

Psychological support

- Patients (n = 40/271) with advanced pancreatic cancer were randomized * to:
 - formal psychotherapeutic support (R/ educational information, a supportive relationship, ongoing psychotherapeutic counseling, emotional and cognitive support to foster "fighting spirit" and to diminish "hope- and helplessness")
 - routine care (on a surgical ward)
- Group 1: survival benefit

*Kuchler et al. JCO 2007

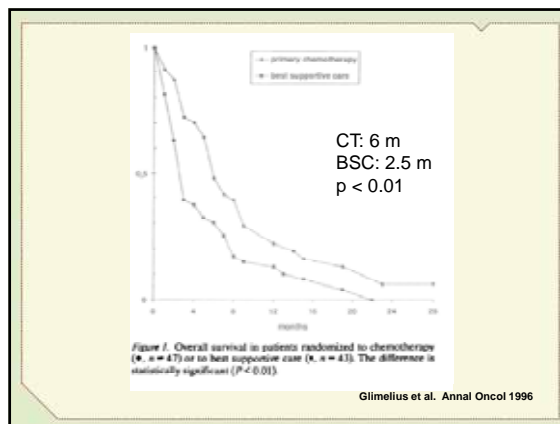
5FU vs. BSC in advanced pancreatic/ biliary cancer

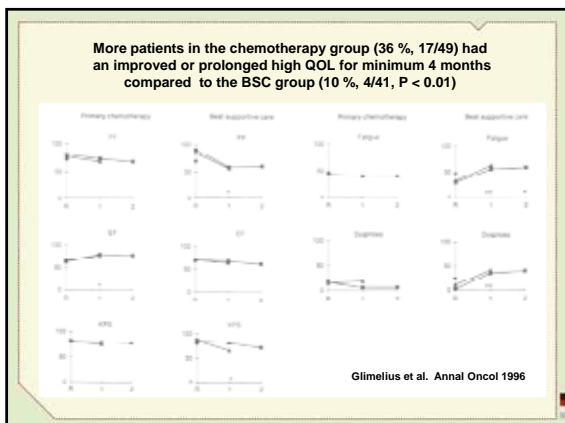
Phase III, 1st line, 90 Patients
Advanced Symptomatic Disease,
Primary Endpoint = overall survival
Secondary endpoints: QOL

RANDOMIZE

- 5FU + LV ± etoposide (n=49)
- BSC (n=41)

Glimelius et al. Ann Oncol 1996





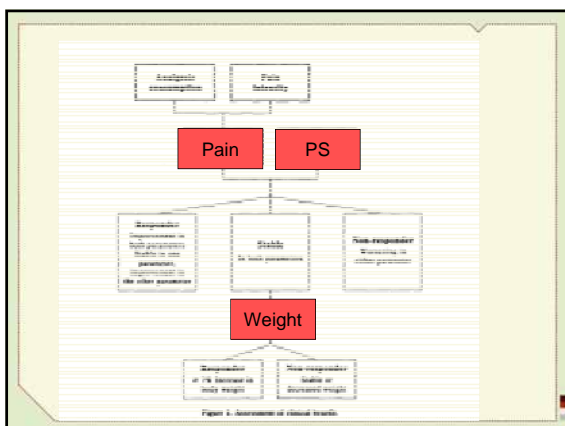
Gemcitabine vs. 5-FU in advanced pancreatic cancer

Phase III, 1st line, 126 Patients
Advanced Symptomatic Disease, KPS 50-90%
Primary Endpoint = "Clinical Benefit Response"
Secondary endpoints: survival, TTP, RR

RANDOMIZE

- GEMCITABINE**
1000 mg/m² weekly x7 for 8 weeks
then weekly x3 every 4 weeks
N = 63
- 5-FU**
600 mg/m² weekly
N = 63

Burris et al. JCO 1997



	5-FU (n= 63)	Gemcitabine (n=63)	p
Clinical benefit response	5%	24%	0.0022
Overall survival	4.41 m	5.65 m	0.0025
1 yr survival	2%	18%	
Response rate	0%	5.4%	
Stable disease	19%	39%	

Burris et al. JCO 1997

Combination of gemcitabine with cytotoxic chemotherapy in advanced pancreatic cancer: phase III trials

Author	N	Treatment	Stage IV %	RR %	PFS / TTP months	OS months
La Roche Lima 2005	360	GEM vs GEM + irinotecan	82	4 / 16	3 / 3.4	6.6 / 6.3
O'Reilly ASCO 2004	349	GEM vs GEM + exatecan	NA	6 / 8	3.8 / 3.7	6.2 / 6.7
Oettle Ann Oncol 05	565	GEM vs GEM + pemetrexed	91	9 / 18	3.6 / 5.2	6.3 / 6.2
Heinemann JCO 2006	195	GEM vs GEM + cisplatin	73	9 / 10	3.1 / 5.3*	6 / 7.5
Poplin ASCO 2006	832	GEM vs GEM FDR vs GEM + oxaliplatin	88	5 / 10 / 9	NA	4.9 / 6.0 / 5.9

Gemcitabine combinations with fluoropyrimidines in advanced pancreatic cancer: phase III trials

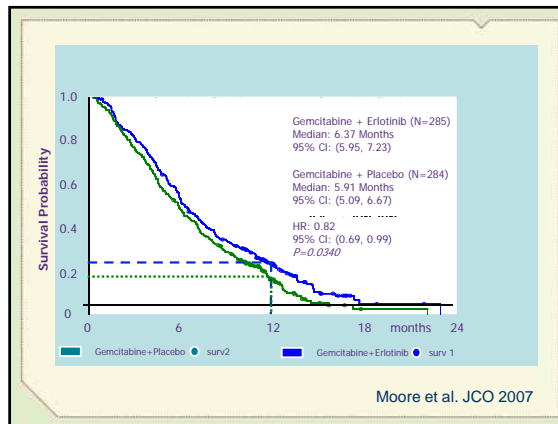
Author	N	Treatment	Stage IV %	RR %	PFS / TTP months	OS months
Berlin JCO 2002	327	GEM vs GEM + bolus 5FU/FA	90	6 / 7	3.2 / 3.4	5.4 / 6.7
Riess JCO 2005	466	GEM vs GEM + 5FU/FA	77	NA	3.5 / 3.5	5.9 / 6.2
Herrmann JCO 2007	319	GEM vs GEM + capecitabine	80	7.8 / 10	3.9 / 4.3	7.2 / 8.4
Cunningham ECCO 2005	533	GEM vs GEM + capecitabine	71	7 / 13	NA	6.0 / 7.4*

*p = 0.026

Combination of gemcitabine with *biologicals* in advanced pancreatic cancer: phase III trials

Author	N	Treatment	Stage IV %	RR %	PFS / TTP months	OS Months
Bramhall Br J Cancer 02	239	GEM vs GEM + marimastat	90	11 / 16	3.1 / 2.2	5.5 / 5.5
Van Cutsem JCO 2004	688	GEM vs GEM + zarneztra	82	16 / 4	3.4 / 3.0	6.3 / 6.6
Moore JCO 2007	569	GEM vs GEM + erlotinib	76	9 / 8	3.6 / 3.8	5.9 / 6.2*

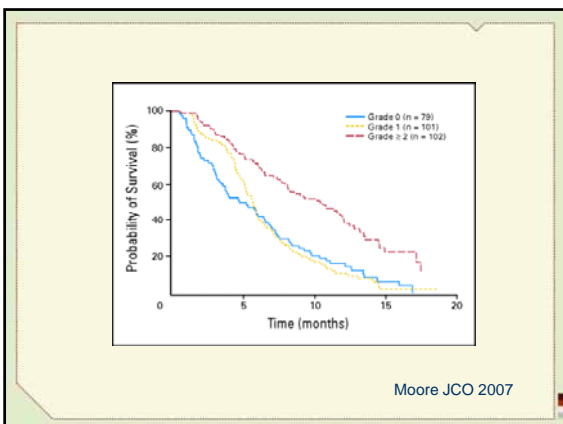
*p = 0.0340



Grade 3-4 toxicity

	Gemcitabine + Erlotinib (N=285)	Gemcitabine + placebo (N=284)
Diarrhea	6 %	2 %
Fatigue	15 %	15 %
Interstitial lung disease	2.1 %	0.4%
Infection	17 %	16 %
Rash	6 %	1 %

Moore et al. JCO 2007



- ### EORTC QLQ-C30
- Questionnaire compliance: >64%
 - No significant difference between two groups
 - Overall QOL idem
 - Individual domains similar, except more diarrhea in group with erlotinib (p < .001)
- Moore et al. JCO 2007

Chemotherapy-Refractory Advanced Pancreatic Cancer

Regimen	N	ORR (%)	MS	Author
Capecitabine/erlotinib	30	10	6.5	Kulke, 2007
Pemetrexed	52	3.8	4.6	Boeck, 2007
Gemcitabine/oxaliplatin	31	23	6	Demols, 2006
Raltitrexed/oxaliplatin	41	24	5.2	Reni, 2006
Oxaliplatin/leucovorin/fluorouracil	30	23	5.7	Tsavaris, 2005
Rubitecan	198	11	3.5	Jacobs, 2004
Irinotecan/oxaliplatin	30	10	5.9	Cantore, 2004
Celecoxib/infusional fluorouracil	17	12	3.4	Milella, 2004
Raltitrexed/irinotecan	19	16	6.5	Ulrich-Pur, 2003
Gemcitabine, fluorouracil, leucovorin, cisplatin	34	24	10.3	Kozuch, 2001
Paclitaxel	18	5	4	Oettle, 2000

Kulke, JCO 2007

Conclusions

- Patients with advanced pancreatic cancer are highly symptomatic and are in need of optimal palliative and symptomatic treatment, including formal psychotherapeutic support.
- QoL represents an important endpoint in clinical studies of chemotherapy for advanced pancreatic cancer. A clinical benefit is achieved in at least 25% of patients treated with gemcitabine.
- More toxicity is not necessarily detrimental for QoL.