OPTIMAL OUTCOMES FOR STUDIES COMPARING BEST SUPPORTIVE CARE WITH CHEMOTHERAPY

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ENDPOINT OF CLINICAL RESEARCH IN ONCOLOGY

TREATMENT EFFECTS ON CANCER

- Complete and partial response
- Response duration
- Time to progression

TREATMENT EFFECTS ON PATIENTS

- Survival
- Quality of life

IS THE NEW TREATMENT BETTER?

Quality of life / Survival	↓	=	↑
↓	NO	NO	?
=	NO	?	YES
↑	?	YES	YES

PHASE III TRIALS WITH CHEMOTHERAPY

Antineoplastic therapy **vs** **placebo**

Antineoplastic therapy **vs** **BSC**

WHAT IS THE BEST SUPPORTIVE CARE?

- Even not clearly defined and standardized best supportive therapy means the best control of the cancer symptoms both in a controlled clinical trials and in clinical practice

BEST SUPPORTIVE CARE VERSUS CHEMOTHERAPY

- **Non Small Cell Lung Cancer (stage IIIB-IV)**
- **Advanced gastrointestinal cancer:**
  - **pancreatic cancer**
  - **gastric cancer**
  - **colorectal cancer**
- **Advanced prostatic carcinoma**

PHASE III TRIALS OF CHEMOTHERAPY VS BSC

- Are not double-blind trials

- The patients know the assigned treatment

Non Small Cell Lung Cancer
Stage IIIB-IV

Chemotherapy vs BSC in NSCLC

Author	N° pts	Treatment	OR	Median OS(mo)	QoL
Thongprasert S, Lung Cancer 1999	287	IEP or MVP+BSC BSC	40.0%	5.9-8.1* 4.1	↑
ELVIS trial JNCI 1999	161	vinorelbine BSC	19.7%	7.0* 5..2	↑ (p= ns)
Anderson H, BJC 2000	300	gemcitabine+BSC BSC	19%	No diff	↑
Ranson M, JNCI 2000	157	paclitaxel+BSC BSC	16%	6.8* 4.8	=
Shepherd FA, JCO 2000	103	docetaxel + BSC BSC	7.1%	7.0* 4.6	↑
Roszkowsky K, Lung Cancer 2000	207	docetaxel + BSC BSC	13.1%	6.0* 5.7	trend ↑

*: statistically significant difference

Use of analgesic drugs and palliative radiotherapy

(Shepherd FA et al, JCO 2000)

	Docetaxel (%)	Best Supportive Care (%)	*P*
Any medication	62	77	.02
Morphine for pain	32	49	.01
Nonmorphine analgesics for pain	39	55	.03
Medications for indications other than pain	30	49	< .01
Radiation	26	37	.09

Use of analgesic drugs and palliative radiotherapy

(Roszkowsky K et al, Lung Cancer 2000)

Parameter	Docetaxel		BSC		*P*-value
	n	%	*n*	%	
Total number of patients	137	100.0	70	100.0	
Patients with palliative radiotherapy during the study					
At least one dose	33	24.1	29	41.4	$P<0.01$
None	104	75.9	41	58.6	
Patients with tumor-related medication during the study					
Opiate analgesic	56	40.9	48	68.6	$P<0.001$
Non-opiate analgesic	44	32.1	43	61.4	$P<0.001$
Tumor-related medication other than for pain	75	54.7	52	74.3	$P<0.001$
Anti-infective medication	79	57.7	29	41.4	$P=0.027$

Advanced Gastrointestinal Cancers

Chemotherapy vs BSC

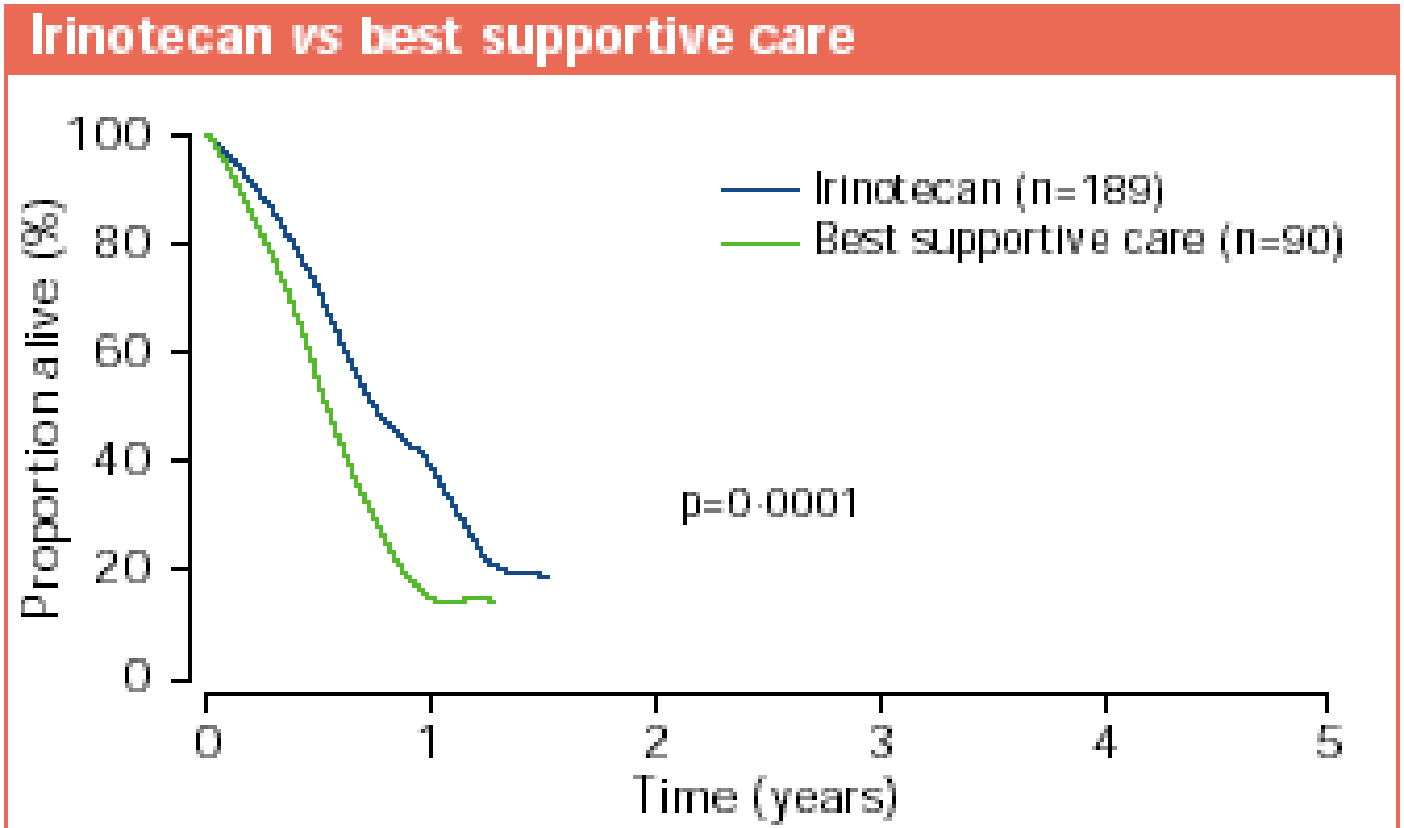
Tumor	N° pts	Treatment	OR	Median OS(mo)	instrument for QoL	QoL
PANCREATIC-BILIAR CA. Ann Oncol 1999	90	FELv or FLv BSC	8%	6.0* 2.5	**EORTC-QLQ-C30**	↑*
GASTRIC CA. Glimelius Ann Oncol 1994	18	FELv or FLv BSC	33%	~10.0* ~5.0	**EORTC-QLQ-C30**	↑*
Pyrhonen S BJC 1995	41	FEMTX BSC	29%	12.3* 3.1	**no**	no data
Glimelius B, Ann Oncol 1997	61	ELF of FLv BSC	nr	8.0 5.0	**EORTC-QLQ-C30**	↑*
Murad AM, Cancer 1993	40	FAMTX BSC	50%	9.0* 3.0	no	**nr**

*: statistically significant difference

Chemotherapy vs BSC

COLORECTAL CARCINOMA	N° pts	Treatment	OR	Median OS(mo)	Strument for QoL	QoL
Cunningham D, Lancet 1998	189	irinotecan + BSC BSC "Second-line" treatment	nr	↑	**EORTC-QLQ-C30**	↑

Overall Survival



Advanced Prostatic Carcinoma

Advanced prostatic cancer

161 pts

Mitoxantrone +
Prednisone

Prednisone

Tannock IF et al, JCO 1996

Advanced prostatic cancer

- **Primary endpoint =** PALLIATIVE RESPONSE defined as a 2-point decrease in pain as assessed by a 6-point scale completed by pts (or complete loss of pain if initially the score was 1) without an increase in analgesic medications and maintained for 2 consecutive evaluations at least 3 wks apart.

Chemotherapy vs "BSC"

PROSTATIC CANCER	N° pts	THERAPY	PALLIATIVE RESPONSE	OS (mo)	Instrument for QoL	QoL
Tannock IF JCO 1996	161	Mitoxant+ Prednisone Prednisone	29% 12%	=	**- LASA** **- PROSQOLI** **- EORTC-QLQ- C30** **- Disease-specific module**	↑*

*: statistically significant difference

PROSPECTIVE RANDOMIZED TRIAL OF DOCETAXEL VERSUS BEST SUPPORTIVE CARE IN PATIENTS WITH NON-SMALL-CELL LUNG CANCER PREVIOUSLY TREATED WITH PLATINUM-BASED CHEMOTHERAPY

Shepherd FA, J Clin Oncol 2000; 18:2095-2103

STUDY DESIGN

-2nd line CT in 204 NSCLC patients previously treated with a platinum based chemotherapy in which patients have been randomized to receive:

- docetaxel 100 mg/m^2 every 21 days (reduced to 75 mg/m^2 after interim safety-data monitoring identified a significantly higher toxic death rate)

-or BSC

-Patients receiving docetaxel were premedicated with oral dexamethasone 8 mg bid for 5 days

RESULTS (efficacy)

	D 75	D 100	BSC
Response rate	5.5	6.3	0
Duration (ws)	26.1	23.9	-
Survival (ms)	7.5	5.9	4.6
1-year survival	37	19	19

RESULTS (% Grade 3-4 toxicity)

	D 75	D 100	BSC
Neutropenia	67	86	-
Anemia	5	16	-
Asthenia	18	22	28

5 toxic deaths with D 100 and 1 with D 75

RESULTS (clinical benefit)

- All quality of life parameters favored docetaxel and patients referred significantly less pain and fatigue

- less worsening of PS from baseline with docetaxel

- Less use of morphine for pain (32% vs 49%) and less palliative radiotherapy (26% vs 37%) with docetaxel

Docetaxel as second-line chemotherapy for non-small-cell lung cancer

Roila F et al, J Clin Oncol 2000; 18: 3738 letter

SHORTCOMINGS OF THE STUDY

- Enrollment: study carried out in 35 centers enrolling 204 pts in a 4-year period (1-2 pts per year). Were these pts consecutively enrolled? Or was there a selection bias in the enrollment?

Authors: difficulties with accrual due to the BSC arm and the exclusion of pts previously receiving paclitaxel regimen (the most frequently used regimen in the US)

SHORTCOMINGS OF THE STUDY

- Sample size and statistical significance levels: two unplanned comparisons of survival were reported, 100 mg/m^2 vs BST (no difference) and 75 mg/m^2 vs BSC (> significant survival with CT)

Due to the low number of pts enrolled (55 vs 49) and the shortcomings of the enrollment the conclusion that the “benefits of docetaxel 75 mg/m^2 outweigh the risk” is not acceptable. Furthermore, many of the reported differences between the two treatments did not reach statistical significance and therefore could be due to chance

SHORTCOMINGS OF THE STUDY

- some statistical analyses non clearly reported (i.e., power of log-rank test used for unplanned comparisons)

- Authors: we agree that a sample size of 104 pts would ordinarily be inadequate to determine that docetaxel is superior to BSC; however, the power of the test becomes irrelevant once a significant difference is observed

SHORTCOMINGS OF THE STUDY

- Heterogeneity: the BSC arm was not standardized; in particular, the use of corticosteroids in pts submitted to docetaxel can have an important influence on pain and fatigue symptoms. This produces a relevant noise in evaluating clinical benefit and quality of life.

- Authors: it would be absolutely impossible to standardize BSC due to the variability of symptoms that might develop in pts with progressive NSCLC

SHORTCOMINGS OF THE STUDY

- Conclusions: due to the shortcomings of the study, its results can be considered, at most, as encouraging for the planning of a trial in which BSC is more standardized

- Authors: not possible to repeat a similar study. Docetaxel should be considered the gold standard for second-line treatment of NSCLC