5th EAPC Research Forum: ESMO-EAPC joint session

Best supportive care versus chemotherapy?
The right question to ask?

Best Supportive Care a faulted methodology in need of standards

Nathan Cherny, Israel: apologizes

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History of Best Supportive Care

The term “best supportive care” (BSC) first appears in a 1988 article reporting on chemotherapy studies in non sma;ll cell lung cancer studies initiated in 1983-84.

Chemotherapy Can Prolong Survival in Patients With Advanced Non–Small-Cell Lung Cancer—Report of a Canadian Multicenter Randomized Trial

By Edna Rapp, Joseph L. Pater, Andrew Willan, Yvon Cormier, Nevin Murray, William K. Evans D. Ian Hodson, David A. Clark, Ronald Feld, Andrew M. Arnold, Joseph I. Ayoub, Kenneth S. Wilson, Jean Latreille, Rafel F. Wierzbicki, and Donald P. Hill

J Clin Oncol 1988;6(4):633-41

Study Design and Treatment

When this study was designed, investigators were approached regarding their recommendations about a "no-chemotherapy" control arm. Many investigators wished to participate in a study with such a control arm, but others found it ethically unacceptable to enroll patients in a trial with a no-chemotherapy option.

Patients on the BSC arm were not to be given chemotherapy, but were given palliative radiotherapy as required for superior vena caval obstruction, hemoptysis, painful osseous metastases, brain metastases, or bronchial obstruction. Antibiotics were used to control infections. Corticosteroids were used to treat hypercalcemia or increased intracranial pressure.

J Clin Oncol 1988;6(4):633-41

What was meant by “BSC”?

- BSC
  - Euphemism for no chemotherapy arm
  - Standard supportive measures
- Best?
  - Noting to indicate that this is different from standard supportive care

“Psycho-linguistics” of BSC

- There is an implication that patients will be given a better level of care than standard supportive care
- Enticement to parties who may have reservations about a no chemotherapy arm
  - Ethical review boards
  - Participating researchers
  - Patients

BSC Studies: In general

Most studies involve poorly responsive cancers

Usually the BSC arm is found to be inferior to the chemotherapy arm with respect to objective tumor response and survival.

Imputed Implication

it is almost always better to receive treatment than to be referred for palliative care.

What was the BSC in these studies?

Lung Cancer

Rapp et al. (1988). CAP or VP vs BSC J Clin Oncol 6(4): 633-41.
Cellerino et al. (1991). Alternating CEP/MTX.VP.CCNU vs BSC J Clin Oncol 9(8): 1453-61.
Leung et al. (1992). Inop patients Chem/RT vs BSC Oncology 49(5): 321-6.
Evans + Le Chevalier (1996). NAV+-CP vs BSC Eur J Cancer 32A(13): 2249-55.
Earle + Evans (1997). Paclitax vs BSC Cancer Prev Control 1(4): 282-8.
Thongprasert et al. (1999). IEP vs BSC Lung Cancer 24(1): 17-24.
Anderson et al. (2000). Gemcitabine vs BSC Br J Cancer 83(4): 447-53.
Roszkowski et al. (2000). Docetaxel vs BSC Lung Cancer 27(3): 145-57.
Shepherd et al. (2000). Docetaxel vs BSC J Clin Oncol 18(10): 2095-103.
Anelli et al. (2001). MMC, VBL, and CP vs BSC Rev Hosp Clin Fac Med Sao Paulo 56(2): 53-8.
Thatcher et al. (2005). Gefitinib vs BSC Lancet 366(9496): 1527-37.
Brodowicz et al. (2006). CP.Gem+Gem vs CP.Gem+BSC Lung Cancer 52(2): 155-63.

Gastrointestinal (Colorectal, Gastric, other) Cancer

Glimelius, B., K. Ekstrom, et al. (1997). ELF vs BSC Ann Oncol 8(2): 163-8.
Cascinu, S., E. Del Ferro, et al. (1995). Octreotide vs BSC. Br J Cancer 71(1): 97-101
Cunningham, D. and B. Glimelius (1999). CPT-11 vs BSC Semin Oncol 26(1 Suppl 5): 6-12.
Van Cutsem, E., M. Peeters, et al. (2007). panitumumab vs BSC J Clin Oncol 25(13): 1658-64.
Starling, N., D. Tilden, et al. (2007). cetuximab/irinotecan vs BSC Br J Cancer 96(2): 206-12.

What was the BSC definition in this study?

A Randomized Trial of Alternating Chemotherapy Versus Best Supportive Care in Advanced Non–Small-Cell Lung Cancer

By Riccardo Cellerino, Diego Tummarello, Francesco Guidi, Pierpaolo Isidori, Marzio Raspugli, Bruno Biscottini, and Giuseppe Fatati

Patients assigned to supportive care (arm B) were evaluated monthly by physical and instrumental examination in the same way as arm A. After 2 months of minimum follow-up, they were defined as having a stable or progressive disease similar to treated patients.

Cellerino et al. J Clin Oncol 1991: 1453-61

What was the BSC definition in this study?

Prospective Randomized Trial of Docetaxel Versus Best Supportive Care in Patients With Non–Small-Cell Lung Cancer Previously Treated With Platinum-Based Chemotherapy

By Frances A. Shepherd, Janet Dancey, Rodryg Ramlau, Karin Mattson, Richard Gralla, Mark O'Rourke, Nathan Levitan, Laurent Gressot, Mark Vincent, Ronald Burkes, Susan Coughlin, Yong Kim, and Jocelyne Berille

Patients randomized to the BSC arm were treated with whichever therapy was judged to be appropriate by the treating physician. This treatment could have included treatment with antibiotics, analgesic drugs, transfusions, and palliative radiotherapy.

Shepherd et al. J Clin Oncol 2000;18:2095-103

What was the BSC delivery in this study?

"The two arms were well balanced with respect to sex, performance status, tumor stage, # prior chemotherapy regimens, best response to prior platinum-based chemotherapy"

Patients randomized to the BSC arm were treated with whichever therapy was judged to be appropriate by the treating physician. This treatment could have included treatment with antibiotics, analgesic drugs, transfusions, and palliative radiotherapy.

„Toxicity"

	Docetaxel 75 mg/m² (n = 55)*				Docetaxel 100 mg/m² (n = 49)*				Best Supportive Care (n = 100)*			
	All grades		Grade 3/4		All grades		Grade 3/4		All grades		Grade 3/4	
Toxicity	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Asthenia	30	54.5	10	18.2	30	61.2	11	22.4	47	47.0	28	28.0
Cardiac	5	9.1	1	1.8	8	16.3	2	4.1	8	8.0	1	1.0
Diarrhea	20	36.4	1	1.8	15	30.6	2	4.1	5	5.0	0	

Toxicity: disease-, or treatment related?

Frequency of grade 3/4 "Toxicity": Treatment adequate?

- **Asthenia G3/4 in BSC: 28%**
- **Nausea G3/4 5%**
- **Other symptoms not assessed**

Symptom management type, quality, intensity, outcomes: not reported

Shepherd et al. J Clin Oncol 2000;18:2095-103

What was the BSC definition in this study?

Open-Label Phase III Trial of Panitumumab Plus Best Supportive Care Compared With Best Supportive Care Alone in Patients With Chemotherapy-Refractory Metastatic Colorectal Cancer

Eric Van Cutsem, Marc Peeters, Salvatore Siena, Yves Humblet, Alain Hendlisz, Bart Neyns, Jean-Luc Canon, Jean-Luc Van Laethem, Joan Maurel, Gary Richardson, Michael Wolf, and Rafael G. Amado

. BSC was defined as the best palliative care per investigator excluding antineoplastic agents.

Van Cutsem E, et al. J Clin Oncol 2007;25:1658-64.

What was the BSC delivery in this study?

Table 2. Any Grade Adverse Events in at Least 10% of Patients and Corresponding Grade 3/4 Events

	Panitumumab Plus BSC (n = 229)						BSC Alone (n = 234)					
	Any Grade		Grade 3		Grade 4		Any Grade		Grade 3		Grade 4	
Adverse Event	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
tients with at least one adverse event - n	229	100	75	33	4	2	202	86	41	18	4	2
ythema	146	64	12	5	0	0	2	1	0	0	0	0
rmatitis acneiform	142	62	17	7	0	0	2	1	0	0	0	0
uritus	130	57	5	2	0	0	5	2	0	0	0	0
in exfoliation	56	24	5	2	0	0	0	0	0	0	0	0
tigue	55	24	10	4	0	0	34	15	7	3	0	0

Toxicity: disease-, or treatment related?

Frequency of grade 3/4 "Toxicity": Treatment adequate?

Asthenia G3/4 in BSC: 2%

Nausea G3/4 1%

Symptom management type, quality, intensity, outcomes: not reported

Symptom assessment: not reported

→ It remains unclear what was „Best Palliative Care"

Van Cutsem E, et al. J Clin Oncol 2007;25:1658-64.

Interim Summary: BSC Definition & Delivery

- Most of these studies represent chemotherapy vs no chemotherapy control arm
- The term BSC care was introduced as a “politically correct” euphemism for the control arm
- Patients seem to receive “stranded” Palliative Cancer Care assessments and interventions (which are not reported)
- The term BEST is inaccurate and misleading
- One can draw no conclusion about the relative merit of systemic therapy versus palliative care from these studies

Evaluation of new (anti-cancer) treatments:
phase I → phase II → phase III (against standard)[1]

What are the standard anti-cancer treatments?

ESMO Guidelines & scientific meetings

ASCO Guidelines & scientific meetings

Applicable for which population?

→ Is this „my“ patient?

PAPER SECTION And topic	Item	Description	Reported on Page #
TITLE & ABSTRACT	1	How participants were allocated to interventions (*e.g.*, "random allocation", "randomized", or "randomly assigned").	✓
INTRODUCTION Background	2	Scientific background and explanation of rationale.	✓
METHODS Participants	3	Eligibility criteria for participants and the settings and locations where the data were collected.	✓
Interventions	4	Precise details of the interventions intended for each group and how and when they were actually administered.	✓
Objectives	5	Specific objectives and hypotheses.	✓
Outcomes	6	Clearly defined primary and secondary outcome measures and, when applicable, any methods used to enhance the quality of measurements (*e.g.*, multiple observations, training of assessors).	✓
Sample size	7	How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules.	✓
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
Statistical methods	12	Statistical methods used to compare groups for primary outcome(s);	✓2
[illegible]	[illegible]	[illegible]	[illegible]
Secondary analyses	18	Address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those pre-specified and those exploratory.	
Adverse events	19	All important adverse events or side effects in each intervention group.	
DISCUSSION Interpretation	20	Interpretation of the results, taking into account study hypotheses, sources of potential bias or imprecision and the dangers associated with multiplicity of analyses and outcomes.	
Generalizability	21	Generalizability (external validity) of the trial findings.	
Overall evidence	22	General interpretation of the results in the context of current evidence.	

Standards of Randomized Controlled Trials: CONSORT

#4 Interventions

Precise details of the interventions intended for each group and how and when they were actually administered

#6 Outcomes

Cleary defined primary and secondary outcome measures and, when applicable, any methods used to enhance the quality of measurements (*e.g.*, multiple observations, training of assessors).

Evaluation of new (anti-cancer) treatments
Who is the „control“ patient with „no“ anticancer treatment option (NACTOP)?

NACTOP

Characterisation of patients with NACTOP
„Palliative Epidemiology“

Symptoms physical
Symptoms psychological
Social needs
Spiritual needs
Decisions – Priorities, information needs
Families
Support networks

→ Systematic data partially available, in clinical trials often collection of „toxicity“ and „quality of life“ data, but not (comprehensive) palliative care assessments.

Assessment and treatment of patients with NACTOP
Development of Cancer Palliative Care

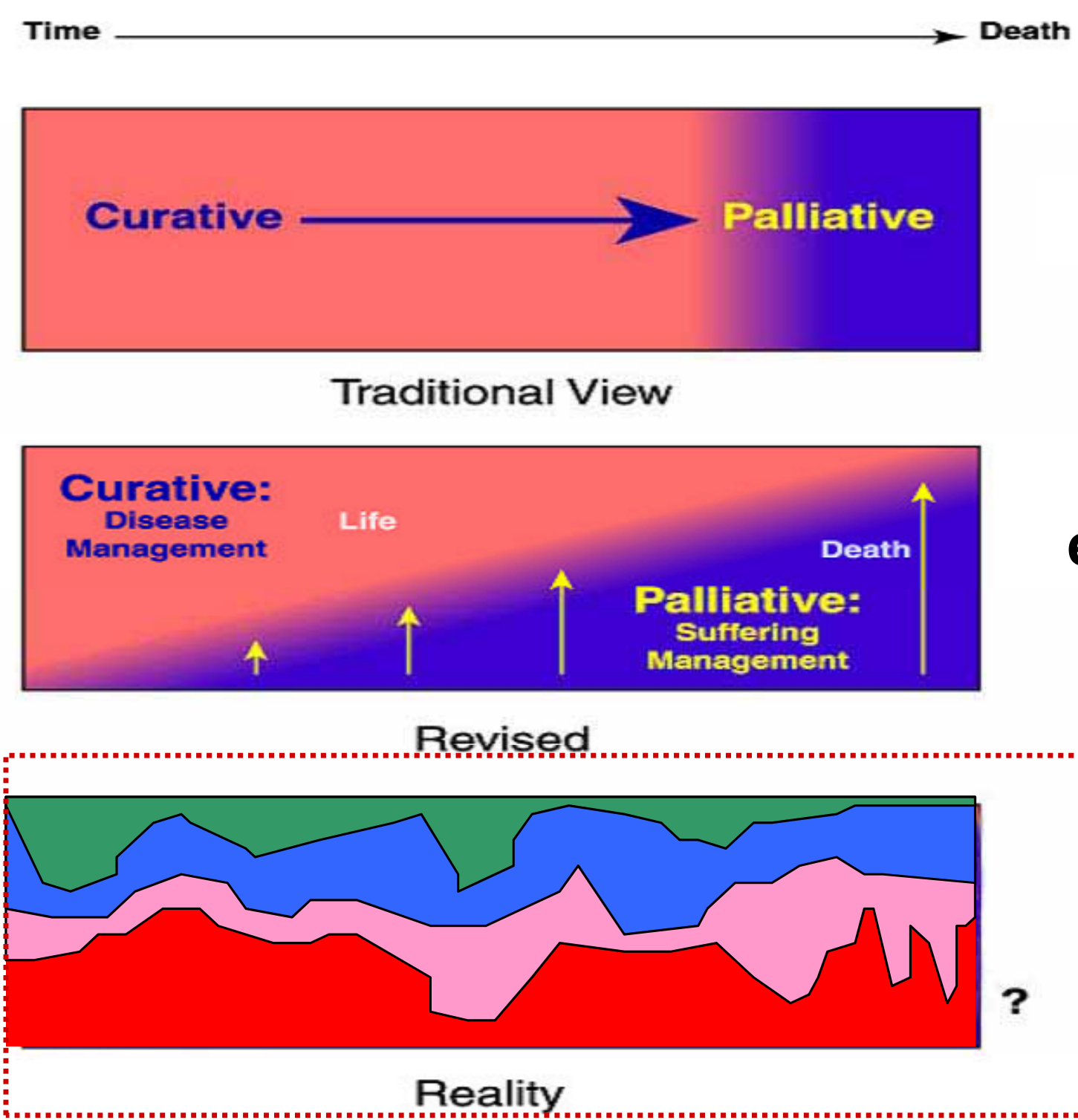
A decade ago palliative care was confined to the last phase of life, "when no anticancer treatment was provided anymore"[1]

Modern oncology in contrast demands for state-of-the-art Palliative Cancer Care integrated in clinical care[2] and also anticancer treatment research[3].

1 ASCO special article. Cancer Care during the last phase of life. JCO 1998;16:1986-96

2 Daugherty CK, et al. Ethical, scientific, and regulatory perspectives regarding the use of placebos in cancer clinical trials. J Clin Oncol 2008;26(8):1371-8.

3 ESMO Criteria designated center for integrated oncology and palliative medicine www.esmo.org



< 1998

evolving

Fluctuating challenges and goals

Assessment and treatment of patients with NACTOP
Key elements of Cancer Palliative Care

- Assessment and management of physical and psychosocial **symptoms** and existential **distress** in patients with advanced cancer, acknowledging symptom interactions, symptom clusters and dealing with complexity.
- **Supportive care** measures to alleviate or prevent side-effects of anticancer interventions and enhance their potential to improve patient-reported outcomes.
- **Anticancer interventions** may improve symptom control, provided that state-of-the-art symptom control leaves gaps or that symptom prevention is the treatment objective.
- Critical help in **decision-making** when facing advanced cancer, initiates and accompanies advanced directive processes including (re-) setting of life goals and priorities, assists in legacy work, and grief and bereavement.
- Active support of **patients' families** throughout the trajectory of advanced cancer, facilitating families' involvement in patient care while at the same time minimizes family burden.
- Professional and continuous **coordination of services** involved in care of advanced cancer patients in inpatient and outpatient settings and at patients' home, to avoid fragmentation of care and allow respite care if needed.
- Competence to diagnose **dying** and utilize interdisciplinary approaches to relief physical, psychosocial, and existential suffering to facilitate a dignified death process.

Assessment and treatment of patients with NACTOP
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Do we have accepted standards of care delivery to offer? (as good as oncologist' standards)

How effective are Palliative Cancer Care interventions?
Importance of qualification of professionals

Several examples:
- surgeons TMR
- Radiotherapists radiochemotherapy
- GP vs HIV-specalist AIDS Mgmt

Oncologists and (self-peceived) Palliative Care Skills

	Agree +	Disagree +
I received good training in PC during my oncology fellowship (residency)	52.8	42.0
Most MOs I know <u>are</u> expert in the management of the physical and psychological symptoms of advanced cancer.	37.5	41.8

ESMO survey

How effective are Palliative Cancer Care interventions?
Importance of qualification of professionals

Who provides Pallative Care to Cancer patients?

1) **a significant proportion of palliative cancer care can be provided by the primary cancer care team**

2) **consultation with palliative cancer care specialists may range from a single consultation about a specific issue to several encounters or ongoing involvement until death and into the period of bereavement.**

ESMO‘ concept of integrated oncology & palliative medicine
EAPC norms of specialist palliative care
ASCO‘s emerging concept of Palliative Cancer Care

How effective are symptom control interventions?
Placebo-controlled studies

Placebo effect	⟷	Effects in the placebo group
Real improvement caused by the drug		Changes resulting from from the natural course of the disease
Little evidence, „hard to study“		Patient‘s hopes or desire not to disappoint the physician More favourably interpretation by an investigator of a physical sign or patient report Other treatments („Best supportive care“) → whole therapeutic environment

Temple RT. Implications of effects in placebo groups. JNCI 2003;95:2-3

How effective are symptom control interventions?
Placebo-controlled studies

Individual responders

Pain (0%-21%)

Appetite (8%-27%)

Weight gain (7%-17%)

QoL (not reported)

Performance status (6%-14%)

→ Placebo effect IS a reality in Palliative Care

Temple RT. Implications of effects in placebo groups. JNCI 2003;95:2-3
Chvetzoff G, Tannock I. Placebo effects in oncology. JNCI 2003;95:19-29

Evaluation of new anti-cancer treatments when no standard treatment is available: A Palliative Cancer Care View of the optimized trial

Symptom and other assessments (beyond QOL) are standardized *(EPCRC?)* **→, training required**

True (!) placebo

Palliative Cancer Care interventions are defined, standardized, and controlled for (Specialists‘ role)

Cancer-related symptoms and syndromes as primary (!) endpoint (Clinical Benefit Response, syndrome-targets [Biomarkers])[1]

1 Köberle D et al, J Clin Oncol 2008; in press

Best Supportive Care a faulted methodology in need of standards: CONCLUSIONS

Work required to provide quality assessments of outcomes relevant in Cancer Palliative Care

Work required to homogenize key cancer-related symptom management approaches

Incorporation of palliative care expertise into "Good clinical practice" certification

→ Integrated Oncology and Palliative Medicine

Thank you!

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