Impact of anti-tumor therapy on symptom control

Present level of evidence and research agenda for the future

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Anti-tumor treatment in symptom control
Treatment modalities

- Interventional/invasive methods
  - Surgery
  - Endoscopic techniques
- Radiotherapy
- Medication
  - Cytotoxic agents
  - Hormones
  - Immune modulators
    - Cytokines
    - Antibodies
  - Vaccines
  - Targeted agents

Anti-tumor treatment in symptom control
Classical study designs

- **Phase I trial**
  - **Toxicity**
    - Dose limiting toxicity
    - Qualitative and quantitative toxicity
    - Maximum tolerated dose (MTD)

    ⟶ Safe dose for phase II trials
- **Phase II trial**
  - Anti-tumor activity
  - Toxicity
    - Early phase II: representative sample of tumor types (early phase II) or a specific tumor type
    - Late phase II: combination with other agents

    ⟶ Stop research and development or to continue in certain tumor types

Anti-tumor treatment in symptom control
Classical study designs

- **Phase III trial**
  - New treatment is compared to standard treatment
  - Goal:
    - Superiority
    - Non-inferiority or equivalence of new treatment

→ Evidence of therapeutic benefit

Anti-tumor treatment in symptom control
Treatment outcome

Target	Parameter	Benefit
Tumour	Response rate	20%
	Time-to-progression	3 months
	CR+PR+SD	Clinical benefit
Patient	Disease-free survival	
	Overall survival	3-5%
	Quality of Life	
Society	Morbidity	
	Economical impact	Costs?
	Mortality	

Anti-tumor treatment in symptom control
Treatment evaluation systems

- **Response**
  - Response Evaluation Criteria in Solid Tumors (RECIST)

- **Adverse events**
  - Common Terminology Criteria for Adverse Events (CTC-AE)
  - RTOG late radiation morbidity scoring scheme
  - SOMA/LENT (Late Effects on Normal Tissue) scale
    - Subjective (patient perception)
    - Objective (grading of objective symptoms by the physician)
    - Management Analytical (laboratory and imaging techniques)

Anti-tumor treatment in symptom control
Treatment evaluation systems

- **Quality of life (cancer-specific)**
  - More accurate evaluation of the well-being of individuals or groups of patients
  - Benefits and side-effects due to medical intervention
  - Scales:
    - EORTC Quality of Life Questionnaires (EORTC QLQ-C30 + Disease-specific modules)
    - Functional Assessment of Cancer Therapy (FACT-G + symptom specific modules)
    - Functional Living Index–Cancer (FLIC)
    - Visual Analogue Scale-Cancer (VAS-C)
    - Profile of Mood States (POMS)
    - Rotterdam Symptom Checklist (RSCL)

Impact of anti-tumor treatment on symptom control

Present level of evidence

Anti-tumor treatment in symptom control
Impact of chemotherapy on QoL/PFS/OS compared to BSC

Tumor type	First-line treatment	Second-line treatment
Non-small cell lung cancer	Platinum-based	Docetaxel
	Vinorelbine	Premetrexed
	Gemcitabine	
	Docetaxel	
	Paclitaxel	
Colorectal cancer	5-Fluorouracil-based	Irinotecan
Pancreatic cancer	Gemcitabine	
Hormone-refractory prostate cancer	Mitoxantrone	
Gastric cancer	5-Fluorouracil-based	

Anti-tumor treatment in symptom control
Impact of chemotherapy: NSCLC

Author (year)	Chemotherapy	All patients			PS2 patients		
		n	Survival (CT *vs*. BSC)	QoL gain	*n*	Survival (CT *vs* BSC)	QoL gain
NSCLC group (95)	CDDP-based CT	778	HR 0.73 NA (*P* <0.0001)	NA	NA	Advantage for CT	NA
Cullen (99) Billingham (00)	MIP	797	CT > BSC (*P* = 0.01)	Yes	159	HR 0.98 NS	Yes
Stephens (02)	CDDP-based	725	HR 0.77 (*P* = 0.0015)	No	147	Advantage for CT (NS)	NA
ELVIS (99)	Vinorelbine	161	HR 0.65 (*P* = 0.03)	Yes	41	6.4 *vs* 1.9 mo	NA
Roszkowsk (00)	Docetaxel	207	CT > BSC (*P* = 0.026)	Yes	41	NA	NA
Ranson (00)	Paclitaxel	157	CT > BSC (*P* = 0.037)	Yes	26	4.1 *vs* 2.9 mo	NA
Anderson (00)	Gemcitabine	300	CT = BSC	Yes	108	3.2 *vs* 2.6 mo	NA

Anti-tumor treatment in symptom control
Impact of second-line chemotherapy: NSCLC

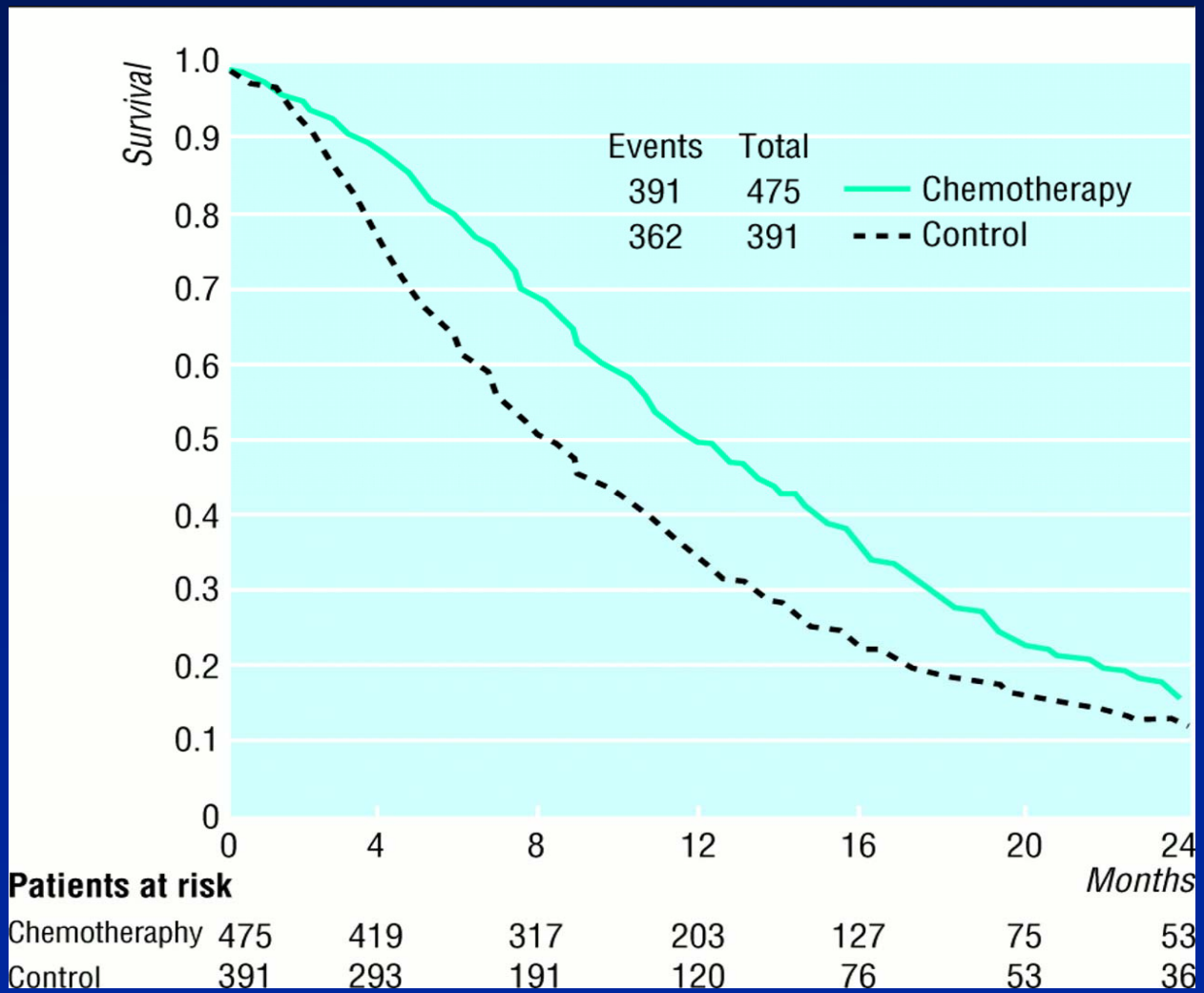
Author	Treatment	No Pts	OR (%)	MS (m)	1-Year S (%)	Qol	P
Shepherd	Docetaxel 75 mg/m²	55	6	7.5	37	CT > BSC	<0.05
	Best supportive care	100	0	4.6	12		
Fossella	Docetaxel 75 mg/m²	125	7	5.7°	32	D > VI	0.025
	Docetaxel 100 mg/m²	125	11	5.5	21		
	Vinorelbine/ifosfamide	123	1	5.6°	19		

Anti-tumor treatment in symptom control
Impact of chemotherapy on symptom control: GI

Author (year)	Tumor type	N pts	QoI gain
Glimelius (95)	GI	61	CT > BSC
Cunningham (98)	Colorectal 2nd-line	189	CT > BSC
Glimelius (92)	Colorectal	43	CT > BSC
Scheithauer (93)	Colorectal	40	CT = BSC if symptoms CT > BSC
Meish (94)	Colorectal	100	CT = BSC

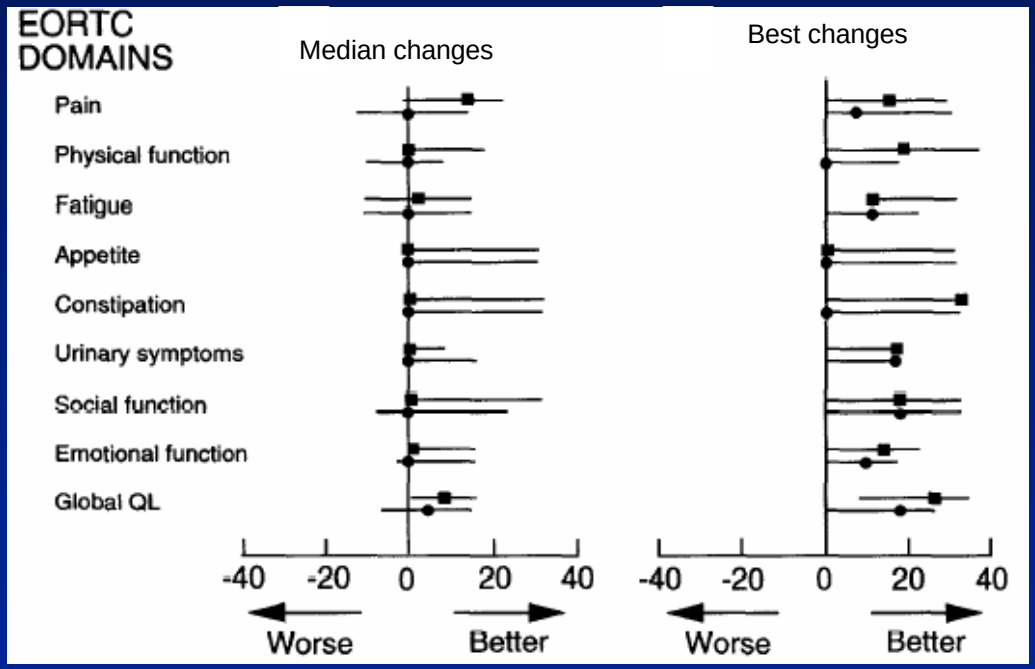
Anti-tumor treatment in symptom control

Impact of chemotherapy on survival: colorectal cancer



Colorectal Cancer Collaborative Group, BMJ 2000

Anti-tumor treatment in symptom control
Impact of chemotherapy on QoL: prostate cancer



Median changes and best changes in EORTC domains that indicate attributes of health-related quality of life

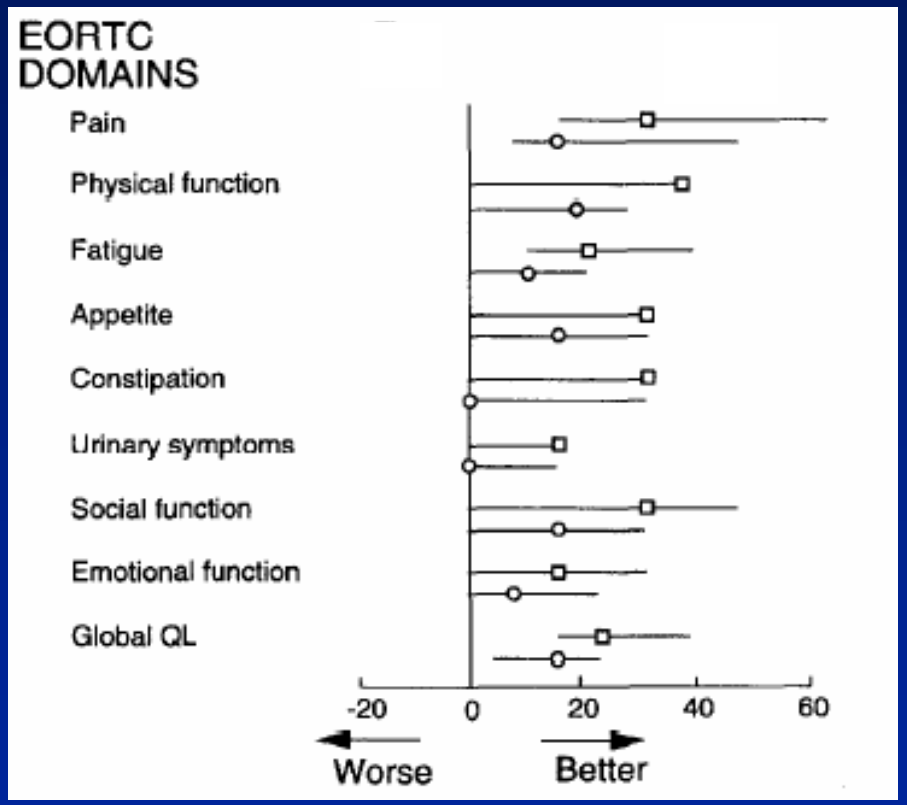
O: Prednisolone; □: mitoxantrone and prednisolone

Tannock et al, J Clin Oncol 1996

Impact of anti-tumor treatment on symptom control

Relation between response and QoL

Anti-tumor treatment in symptom control
Impact of response on QoL: prostate cancer



O: Median change; □: best change in responding patients

Tannock et al, J Clin Oncol 1996

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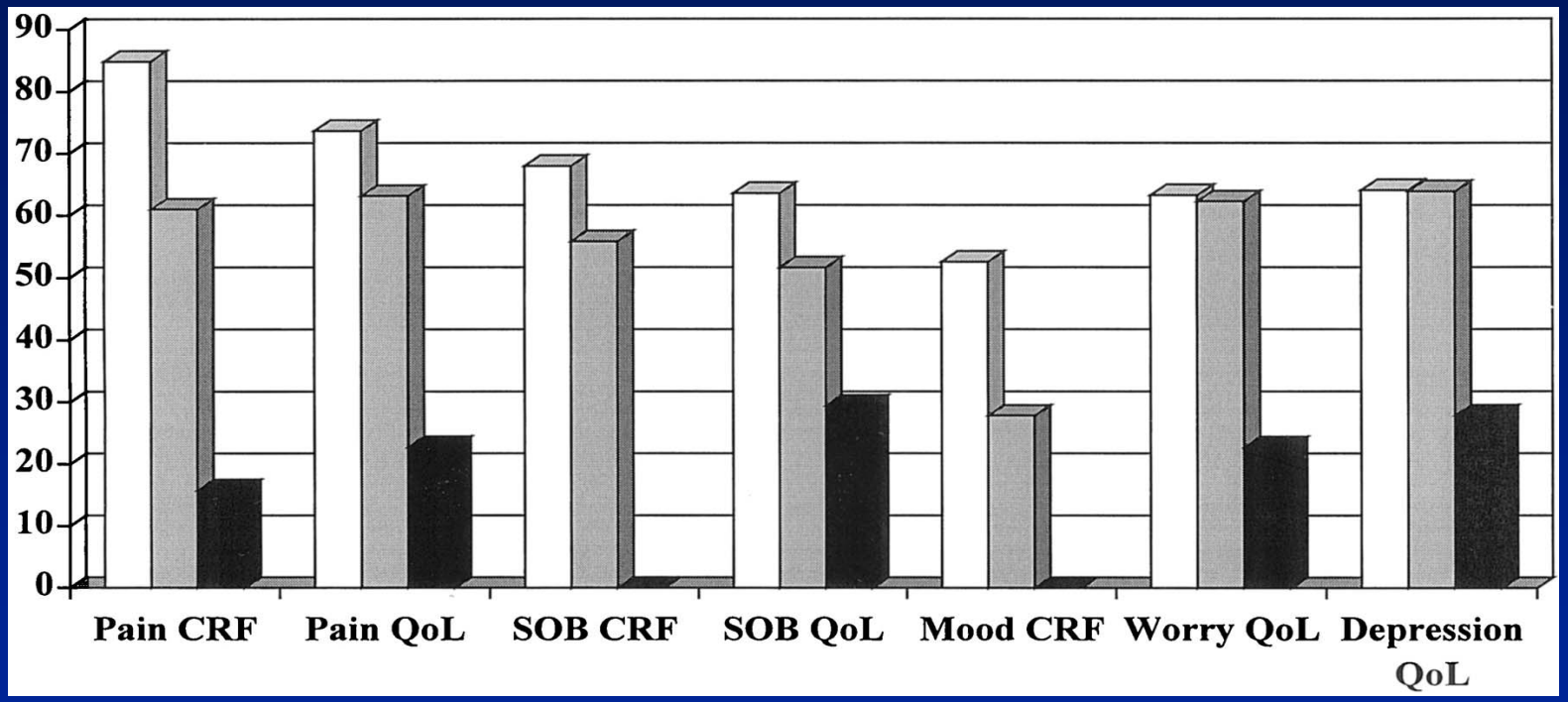
Impact of response on QoL: breast cancer



Proportion of patients with symptom response according to objective response category

Geels et al, J Clin Oncol 2000

Anti-tumor treatment in symptom control
Relationship tumor and symptom response

Pooled Means, Standard Deviations, and Ranges for Demographic and Clinical Variables across 21 Studies (Overall $n = 2629$)

Demographic and clinical variables	Mean (standard deviation)	Range	No. of studies
Age in yrs	55.7 (7.37)	42–68	20
Gender			
Male	51%		21
Treatment duration in mos	9.1 (9.4)	1–24	19
Study duration in mos	4.3 (3.1)	1.5–17.5	20
TR rate	41% (17%)	16–79%	21
TR duration in mos	6.2 (3.6)	2.5–17.5	15
SR rate	64% (20%)	38–96%	21
CR/PR	75% (22%)	16–99%	21
SD	64% (22%)	23–93%	12
PD	40% (31%)	6–93%	18
SR duration in mos	3.8 (1.3)	1.5–5.6	9
Survival in mos	9.8 (3.6)	5–15	11

TR: tumor response; SR: symptom response; CR/PR: complete/partial response; SD: stable disease; PD: progressive disease.
Pooled means were obtained by computing the average median values for each of the 21 studies.

Victorson et al, Cancer 2006

Impact of anti-tumor treatment on symtom control

Research agenda for the future

Anti-tumor treatment in symptom control
Research for the future: patient selection

- Comprehensive geriatric assessment

Parameter	Elements of the Assessment
Functional status	Performance status
	ADL
	IADL
Co-morbidity	Number of co-morbidities
	Severity of co-morbidities
	Co-morbidity index or scale (eg, Charlson Comorbidity Index, Cumulative Illness Rating Scale–Geriatrics)
Socioeconomic status	Living conditions
	Presence and adequacy of a caregiver
	Income
	Access to transportation
Cognitive status	Folstein's Mini-Mental Status
	Other tests
Emotional status	Geriatric Depression Scale
Polypharmacotherapy	Number of drugs assumed
	Appropriateness of medications
	Risk of drug interactions
Nutritional status	Mini-Nutritional Assessment
Presence of geriatric syndromes	Dementia, delirium, depression, falls, neglect and abuse, spontaneous bone fractures, failure to thrive

Anti-tumor treatment in symptom control
Research for the future: patient selection

- Groningen Frailty Indicator

Parameter	Question
Mobility	Can the patient without help do
	1. Shopping (yes: 0; no: 1)
	2. Walk outside (yes: 0; no: 1)
	3. Dress and undress (yes: 0; no: 1)
	4. Use the toilet (yes: 0; no: 1)
Physical fitness	5. How many points gives the patient for his fittness (1-6: 1; 7-10: 0)
Vision	6. Has the patient problems in dialy living due to his vision (yes: 0; no: 1)
Hearing	7. Has the patient problems in dialy living due to his hearing (yes: 0; no: 1)
Nutrition	8. Has the patient unwillingy lost 3 kg in 1 or 6 kg in 6 months (yes: 0; no: 1)
Co-morbidity	9. Uses the patient actually 4 or more different medications (yes: 0; no: 1)
Cognition	10. Has the patient problems with his memory (or known dementia) (yes: 0; no: 1)
Psychosocial	11. Has the patient a feeling of emptyness (yes: 0; no: 1)
	12. Misses the patient people around him/her (yes: 0; no: 1)
	13. Does the patient feel abandonned (yes: 0; no: 1)
	14. Does the patient feel depressed (yes: 0; no: 1)
	15. Is the patient nervous or anxious (yes: 0; no: 1)

Frail if score is 4 or more

Anti-tumor treatment in symptom control
Research for the future: predicting tumor response

- Predictive factors = variables that can account for the expected outcome of a specific intervention

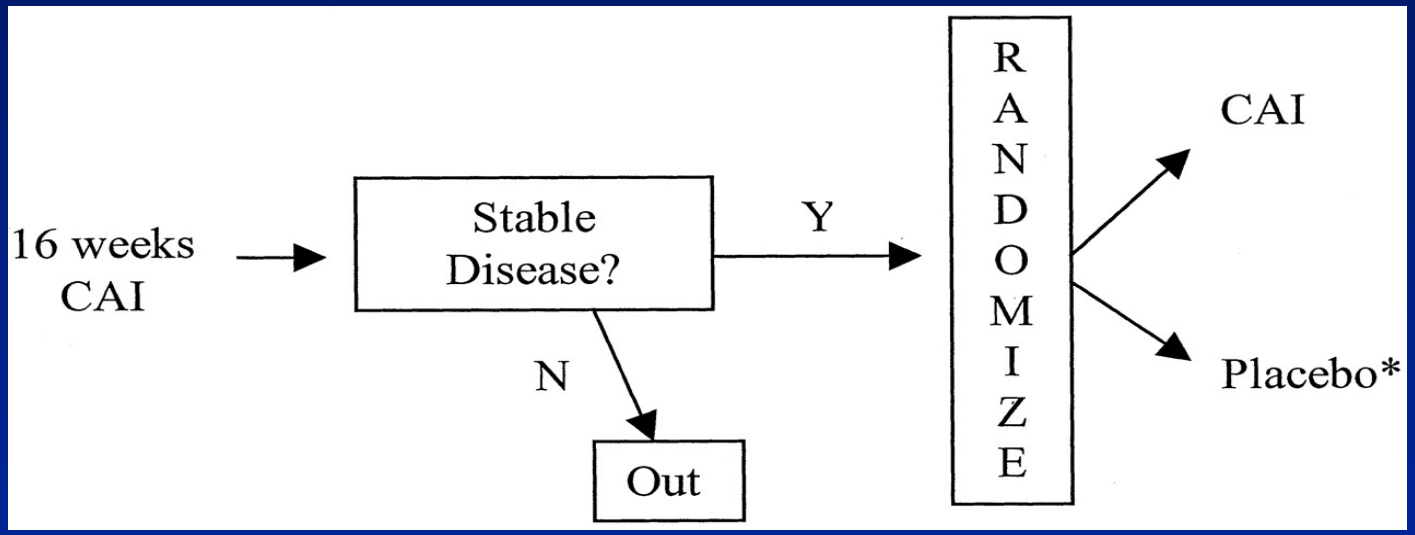
- Current available factors
  - Breast cancer
    - HER2-neu: trastuzumab/anthracyclines
    - Estrogen-progesteron receptor: tamoxifen
  - non-Hodgkin lymphoma
    - CD20: rituximab
  - Gastro-intestinal stromal tumour
    - c-KIT: imatinib
  - CML
    - Ph chromosome: imatinib

Anti-tumor treatment in symptom control
Research for the future: evaluation treatment outcome

- New endpoints
  - Biological response
  - Biomarkers
- New evaluation instruments
  - PET-scan/MRI
  - QoL/symptom evaluation scales

Anti-tumor treatment in symptom control
Research for the future: new study designs

- Randomized continuation design



Anti-tumor treatment in symptom control
Conclusion

- Anti-tumor treatment may be used in symptom control and for improvement of quality of life

- New research topics for the future are
  - Patient selection
  - Predictive factors for tumor response
  - Development of new less toxic drugs (targeted drugs)
  - New endpoints
  - New trial design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