Presented
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Slides
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Time to Progression

Should TTP be a primary efficacy endpoint for first line chemotherapy trials in metastatic breast cancer?

Breast Cancer Cytotoxic Drugs FDA Approved

• Methotrexate	1953
• Cyclophosphamide	1959
• Thiotepa	1959
• Vinblastine	1961
• 5-Fluorouracil	1962
• Doxorubicin	1974
• Paclitaxel	1994
• Docetaxel	1996 1998
• Capecitabine	1998

Time to Progression

- Time to treatment failure used in 1970's - 1990's
- Calculated from date of randomization until progressive disease or death
- ? censor at further antitumor treatment

Time to Treatment Failure

Calculated from date of randomization until

- PD
- Death
- Withdrawal due to adverse event
- Patient referral
- Lost to follow-up
- Further antitumor therapy

Survival as Endpoint

Pro

- Easily measured at anytime
- Ultimate patient benefit

Survival as Endpoint

Con

- Medians range from 10-47 mo
- Secondary treatment affects outcome
- Literature suggests small survival benefit with most active agents (2-6 months)
- May not be directly related to treatment

Time to Progression as Endpoint

Pro

- Related directly to treatment
- Short follow-up
- Patient benefit - relief or delay of symptoms or complications

Time to Progression as Endpoint

Con

- Difficult to measure
- Dates often difficult to determine, dependent on time of evaluation
- Rules often not prospectively defined
- May not be a surrogate for patient benefit if toxicity increased
- Confounded by continuous treatment

First Line Treatment for MBC

		No of Patients	TTP (mo)	Survival (mo)
• Engelsman	Classic CMF	125	9	17
	IV CMF	129	5.5	12
			p = 0.000	p = 0.016
• Tormey	CAFVP	107	7	19
	CMFVP-I	109	5	13
	CMFVP-C	86	5	16
			p = 0.03	p = 0.02
• Tormey	CMF	79	5.3	14.5
	AV	166	5.7	13.7
	CMFP	86	9.1	16.4
			p = 0.04	p = 0.03

Humanized Anti-HER2 Monoclonal Antibody

	No of Patients	TTP (mo)	Survival (mo)
Herceptin + chemo	235	7.2	25.4
chemo	234	4.5	20.9
		p < 0.0001	p = .045
H + paclitaxel	92	6.7	22.1
Paclitaxel	96	2.5	18.4
		p < 0.0001	
H + AC	143	7.6	33.4
AC	138	5.7	24.5
		p < .002	

Metastatic Breast Cancer
First Line Therapy
ECOG 1193 - 739 Patients

	RR %	TTF (mos)	Survival (mos)	QOL
Paclitaxel (P)	34	5.9	20.1	NS
Doxorubicin (D)	36	6.2	22.2	NS
P + D	47	8.0	22.4	NS

Sledge, Proc Am Soc Clin Oncol 16:20.1a, 1997 [abs 2]

Does Chemotherapy Improve Survival in Patients with Metastatic Breast Cancer?

A'Hern Meta-analysis of DOX in Cooper-type Regimens in 5 Trials

	RR	TTF	S
HR	0.56	0.69	0.78
95% CI	(0.43 - 0.73)	(0.59 - 0.81)	(0.67 - 0.90)
p value	< 0.001	< 0.001	< 0.001

A'Hern, Br. J. Cancer 67: 801-805, 1993

Randomized Clinical Trials for Metastatic Breast Cancer

- 189 trials - 1/75 - 12/97
  Medline and Embase
- 31,510 women
- 12 therapeutic comparisons
- Tumor response rates, mortality hazards ratio (HR) and severe side effects as outcome measures.

Fossati, et al JCO 16: 3439-60, 1998

Review of Randomized Trials Anthracycline Versus No Anthracycline

- 22 First Line RCT's
- 9 Trials (10 comparisons) Contain TTF or TTP Data
  - TTP and survival = in 7 trials
  - ↑ TTF or TTP and ↑ survival in 2 trials
  - ↑ TTP and = survival in 1 trial

Second Line Treatment for MBC

		No of Pts	TTP (mo)	Survival (mo)
• Jones	Vinorelbine	115	3	8.8
	Melphalan	84	2	7.8
			p < .001	p = .034
• Cowan	Doxorubicin	117	10.5	10.5
	Bisantrene	128	10	9.6
	Mitoxantrone	120	5.9	5.9
• Nabholtz	Docetaxel	203	4.7	11.4
	MV	189	2.7	8.7
			p = .001	p = .0097
• Nabholtz	Paclitaxel			
	175 mg/m^2	235	4.2	11.7
	135 mg/m^2	236	3.0	10.5
			p = .027	p = .321

Asymptomatic Patient - CR With 6 Cycles DOX (161 Patients)

Rx ----------→Survival
TTP 18.7 mo 32.2 mo

OBS → Rx →
TTP 7.8 mo. 28.7 mo.

$p < .0001$ $p = .74$

Falksen, JCO 16: 1669-1676, 1998

Continuous Versus Intermittent Treatment for Advanced Breast Cancer

	Response	TTP	Survival
Cont	49%	6.0 mo	10.7 mo
Int	32%	4.0 mo	9.4 mo
	p = 0.02	RR 1.8 95% CI (1.4-2.4)	RR 1.3 95% CI (.99-1.6)

Coates NEJM 317: 1490-1495, 1987

Symptomatic Patient

Continuous Rx ↑ QOL + toxicity →

Int Rx → ↓ QOL Rx toxicity →

Coates NEJM 317: 1490-95, 1987

Quality of Life
Coates Trial

LASA Scores

- Cont and Int Improved for first 3 cycles
- Int after 3 cycles worse scores for
  - Δ Physical well-being (↓ 23%)
  - Δ Mood (↓ 25%)
  - Δ Appetite (↓ 12%)
  - Δ QOL index - patient (↓ 14%)
  - Δ QOL index - doctor (↓ 16%)
- Change in QOL scores predictive of survival

Conclusions

- Survival benefit with active drugs modest - 2-6 months
- TTP correlates with survival
- ↑ TTP correlates with ↑ QOL
- Accurate reporting of endpoints essential

White Paper - JCO 1991

"The clinical usefulness of a drug must reflect the relationship of risk to benefit for specific clinical conditions."

"The primary aim of cancer treatment is prolongation of life, but the demonstration that a new agent causes tumor regression and improves patients' clinical condition also supports approval of a new agent, even in the absence of improved survival."

"In breast cancer a large fraction of recurrences are symptomatic, making improved DFS a valid surrogate for improved QOL."

O'Shaughnessy, et al. JCO 9: 2225-2232, 1991

Time to progression

is an

acceptable endpoint

which confers patient benefit