

Systemic therapy for breast cancer in the brain: future potential

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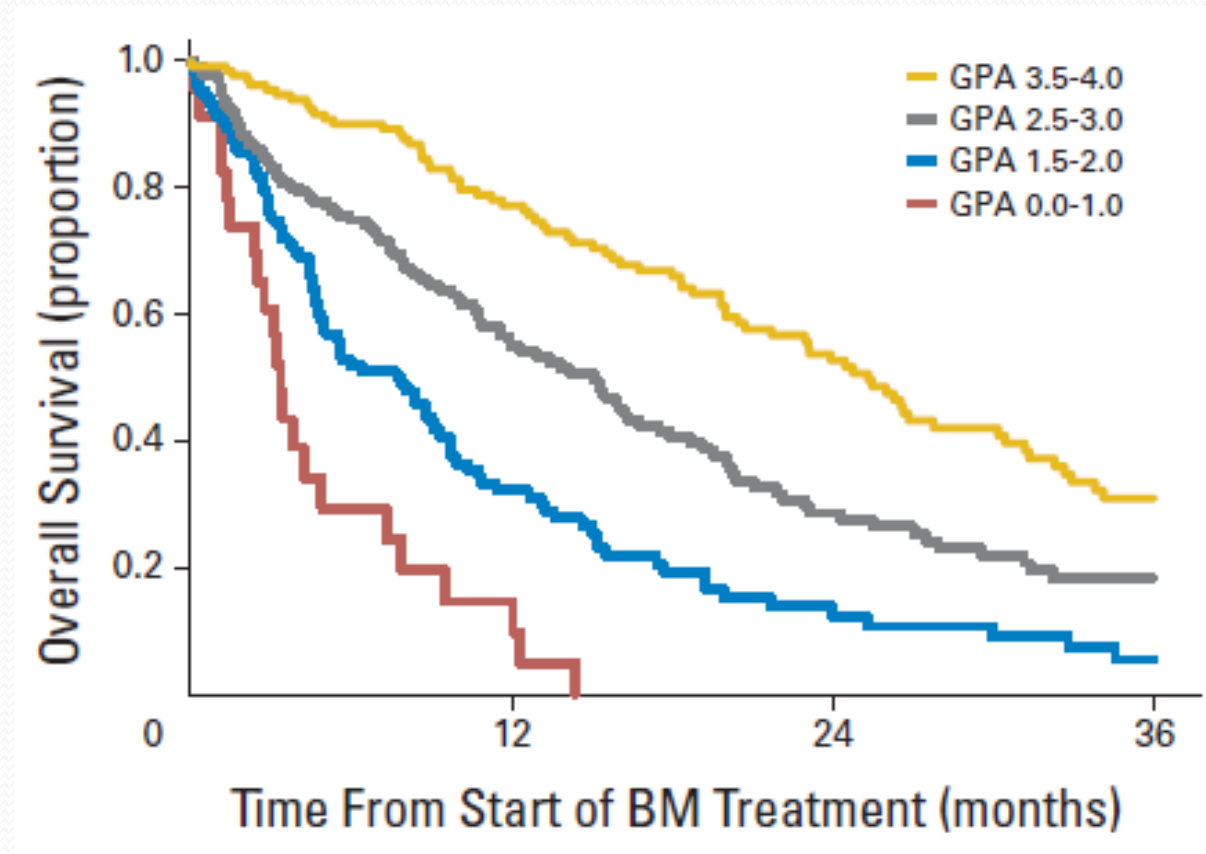
Brain metastases from breast cancer

- Clinical challenge
- Relatively common: up to 30% of stage IV patients at autopsy
 - Clinically presents mostly in HER2+ and TN disease
- Prognosis better than for some other cancers:

Diagnosis	Overall		No. of Patients
	Survival Time		
	(months)		
	Median	95% CI	
NSCLC	7.00	6.53 to 7.50	1,833
SCLC	4.90	4.30 to 6.20	281
Melanoma	6.74	5.90 to 7.56	481
RCC	9.63	7.66 to 10.91	286
Breast cancer	13.80	11.53 to 15.87	400
GI cancer	5.36	4.30 to 6.30	209
Other	6.37	5.22 to 7.49	450
Total	7.16	6.83 to 7.52	3,940

Prognostic models

- ~ 4 000 patients
 - KPS
 - Subtype
 - Age



Prediction of their occurrence

- MDA series:
 - 362 developing brain mets out of 2 136 patients with MBC (< 10 yr f/up)
 - Median time of 8.9 months from stage IV disease (1 – 98m)
 - Multivariate analysis: independent predictors
 - Young age
 - High grade
 - Short DFI
 - More non-CNS sites of metastasis
 - Subtyoe
 - NOT predicted by T stage, N stage, LVI,

What is the role of systemic therapy?

- Posner
- Single patient studies, and other small series in the 1970s onwards
 - Sporadic responses to
 - Anthracyclines
 - Platinums
 - High dose chemotherapy

State of the Art

- Drugs: BLOOD-BRAIN Barrier
 - Few hard data
 - SCLC: 27% response rate to brain mets during systemic therapy for systemic disease....
- How much is efflux pump vs barrier to entry?
- Evidence that some drugs can have higher CNS met concentrations (paclitaxel)
- Interstitial pressure problems for drug access

State of the Art

- Drugs: BLOOD-BRAIN Barrier
 - 5-FU
 - MTX
 - anthracyclines
 - Lapatinib vs Herceptin
 - Temozolamide – poor response in breast
- trade off:
 - QoL/OS
 - hair loss
 - cognitive dysfunction

HER2+ve disease

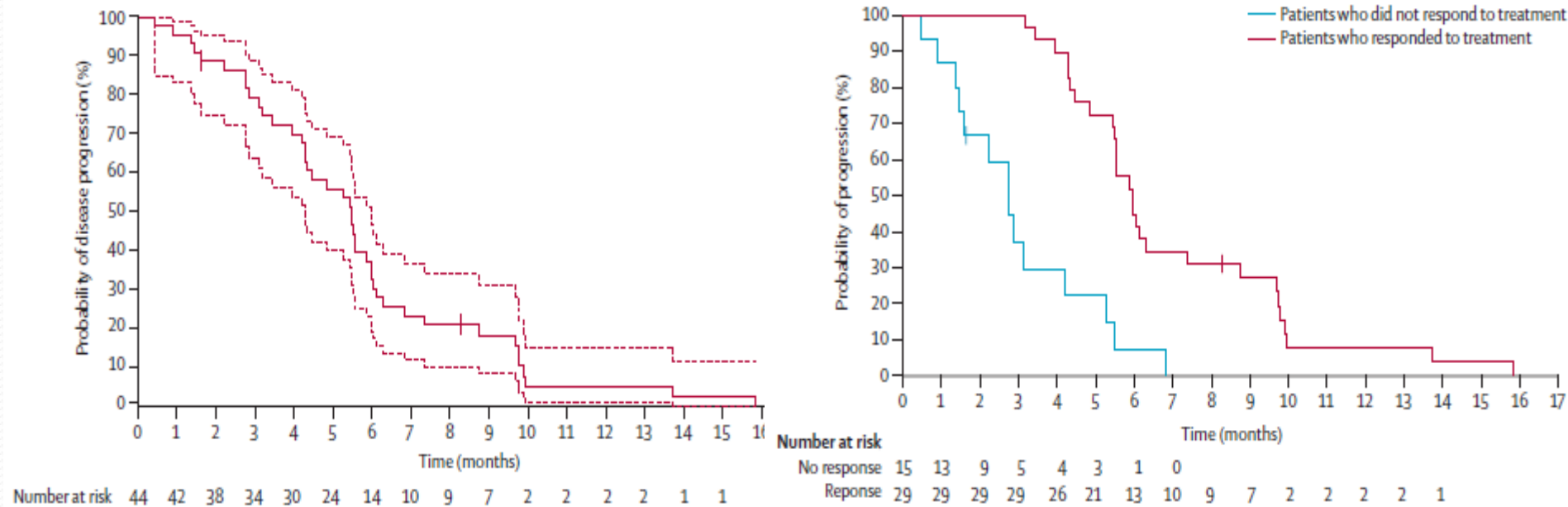
- Adjuvant studies
 - Some concern of an increased rate..
 - Subsequent analysis from HERA trial of CNS as first AND subsequent sites of metastases refutes this.

	1-year trastuzumab group	Observation group	Overall
Cohort of 3401 enrolled patients			
Number of patients	1703	1698	3401
CNS relapse as first DFS event	37 (2%)	32 (2%)	69 (2%)
Time to CNS relapse (years)	1.31 (0.53-2.03)	1.25 (0.53-2.13)	1.26 (0.53-2.03)
Other first DFS event	326 (19%)	421 (25%)	747 (22%)
Cohort of 413 patients who had died and for whom forms were returned			
Number of patients	186	227	413
Died with CNS relapse	88 (47%)	129 (57%)	217 (53%)
Time to CNS relapse (years)	2.11 (1.34-2.99)	1.89 (1.15-2.92)	2.02 (1.19-2.93)
Died without CNS relapse	98 (53%)	98 (43%)	196 (47%)

Data are n, n (%), or median (IQR). DFS=disease-free survival.

Landscape trial

- Phase II of capecitabine+Lapatinib



Clearly active.....and suggests that sensitivity to systemic therapy is clinically relevant

Landscape trial II

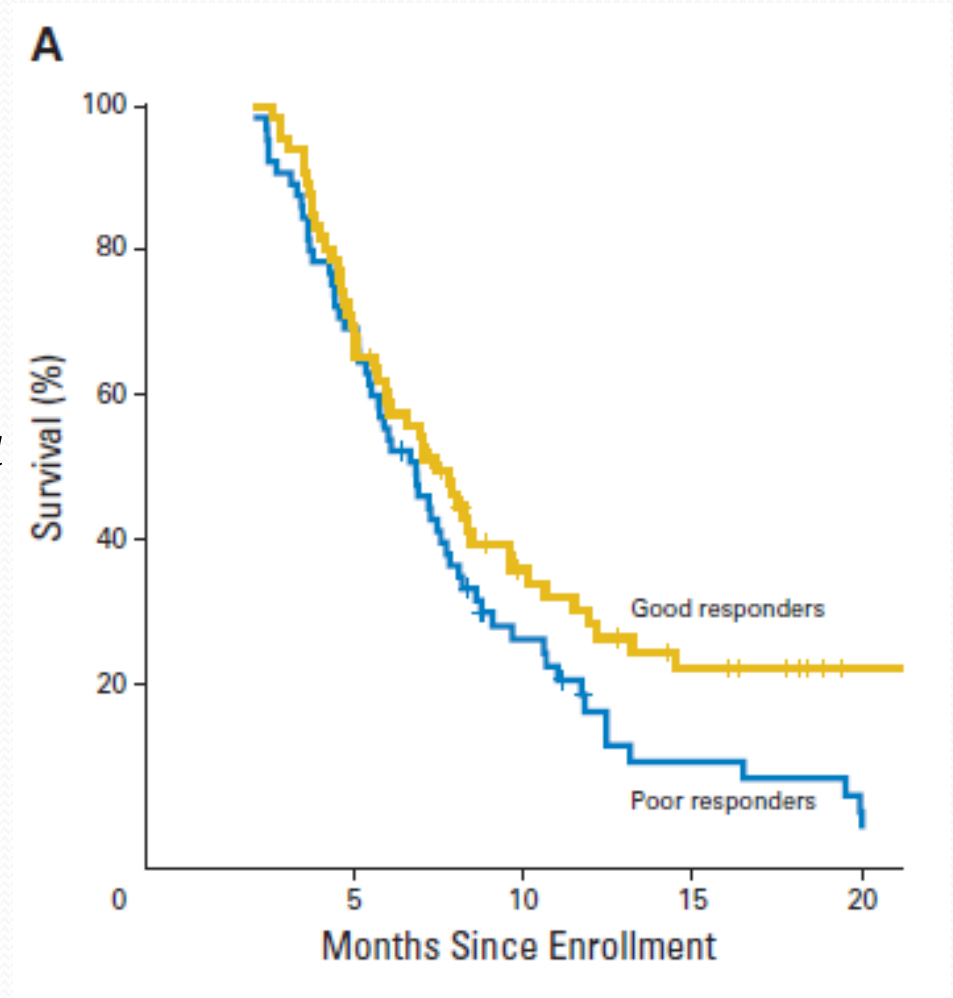
- 5% complete radiological response
- 50% partial response
- 75% progressed first in CNS...

Triple negative

- No real targeted agents....no different in brain
- Interest in
 - PARPinhibitors
 - Other small molecules...

Can we learn from other data?

- Palliative radiotherapy
- How long does it work in other sites – bone?
- Median time to progression of systemic therapy is usually months...



Good outcomes

- Stereotactic radiotherapy
- Neurosurgery

Are brain metastases different?

- Search for biomarkers of brain metastases
 - A number of studies have identified some markers
 - Do they alter propensity for this site?
 - Do they alter the sensitivity to therapy?

Future hopes

- A number of studies have tested the addition of another agent (Efaproxiral ; motexafin gadolinium ;...)

Prevention?

- Two small studies of whole brain radiotherapy
 - France & Scotland (Entente Cordiale)
- Scottish one (Canney et al) numerical advantage in favour of prophylactic WBT
- DRUGS or XRT ?
 - preventive compounds: invasion/escape bloodstream
 - avoidance of immune system
 - target colonization processs (SRC, FAK)
- RANDOMISATION
 - placebo vs. DRUG
 - measure *time to occurence of brainmets*
 - survival + QoLbenefit

Possible agents?

Dasatinib SRC inhibitor

Phase II study with AI @ SABCS 2013

Denosumab RANKL inhibitor

Smith 2012

longer time to occurrence bonemets

Pazopanib multikinase inhibitor MEK, ERK, ckit

longer brainmets free survival in HER+

GSK 461364^a Plk1 inhibitor, radiosensitizer

Qian 2011

CNS disease

- Leptomeningeal is even more of a challenge
- Prevention has to be the primary target
- Therapy options limited but the picture is not as bleak as it was....



LE FROGLET