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Closing remarks and treatment guidelines

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Abstract

The human epidermal growth factor receptor HER2 or C-erbB-2/neu is a tyrosine kinase membrane receptor, which when activated, induces a phosphorylation cascade in cytoplasmic kinases leading to increased protein transcription and cellular growth. HER2 plays an important role in the biology of breast cancer, an observation that has led to the selection of HER2 as a potential target for breast cancer treatment. Trastuzumab (Herceptin®) is the first anti-HER2 monoclonal antibody that has shown a survival benefit in metastatic breast cancer patients with HER2-positive tumours (Norton *et al.*, *Proc ASCO* 2000 **18**, 127a (abstract 483)). Tumour HER2 status should no longer be ignored because of its direct implications for the optimal management of breast cancer patients. A high priority for future research is to refine and standardise HER2 testing in order to minimise false-negative results. Furthermore, this procedure would overcome current issues relating to test reproducibility between pathology laboratories and definitions of HER2 positivity. In the meantime, a HER2-positive status on testing using any approved technique has implications for clinical practice (Fig. 1). The treatment algorithm given in Fig. 1 considers the lack of level 1, evidence-based studies that demonstrate convincingly the value of HER2 as a predictive marker for resistance or sensitivity to classic forms of breast cancer therapy (Piccart *et al.*, *Eur J Cancer* 2000, **36**, 1755–1761). In addition, the algorithm incorporates the available data from 1999–2000, which were generated from prospective trials exploring the value of trastuzumab both as a single agent and in combination with chemotherapy. © 2001 Published by Elsevier Science Ltd.

Keywords: Monoclonal antibody; Breast cancer; HER2

1. Treatment of advanced disease

1.1. Endocrine therapy

Patients with an oestrogen receptor (ER)- and HER2-positive tumour should not be denied endocrine therapy [1]. However, in view of the possible limited value of hormonal agents when HER2 is co-expressed with ER or progesterone receptors (PgR) [2–4] patient progress should be followed closely. Clinical trials are currently investigating the combination of trastuzumab (Herceptin®) with endocrine therapy in ER/HER2-positive tumours and their results should become available in the next 2 years.

1.2. Trastuzumab for whom, when and how?

There is growing retrospective evidence that patients who benefit from trastuzumab treatment are the ones with strong HER2 overexpression (3+ by immunohistochemistry = IHC) or with HER2 amplification (more than two copies of the gene, as assessed by fluorescent *in situ* hybridisation (FISH)).

Table 1 illustrates outcomes in the pivotal trial of chemotherapy±trastuzumab according to the IHC score (2+ or 3+) and strongly suggests that the benefit gained from the addition of trastuzumab to first-line chemotherapy is largely confined to the 3+ subset [5].

Table 2 provides data from a similar subset analysis carried on in the trastuzumab monotherapy trials, and here also, benefits in terms of objective response rates are seen almost exclusively in HER2 3+ patients [6].

HER2 testing by FISH is substantially more expensive than HER2 testing by immunohistochemistry (IHC). Nevertheless, it is gaining in popularity and the data, so far, suggest (1) good concordance with overexpression by IHC (Table 3) [7], (2) good prediction of outcome of trastuzumab therapy (Table 4) [8]. Given this background, it is reasonable for the time being, to offer trastuzumab therapy to all patients with a 3+ score by IHC and to patients with a 2+ score if they are found to be FISH+. Further research is clearly needed

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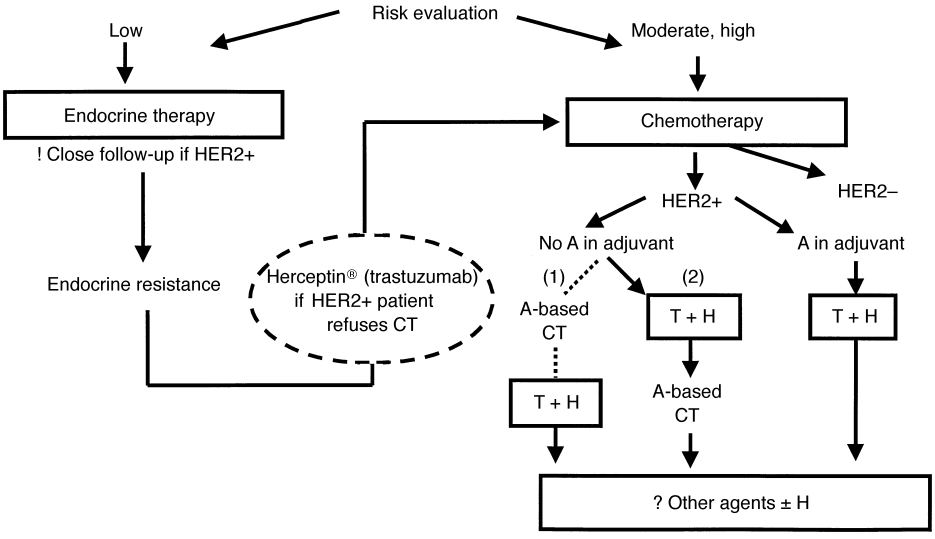

Fig. 1. Proposed pattern of systematic management of HER2- positive metastatic breast cancer patients. (1) 'Conservative' sequence in line with current labelling of H. (2) Innovative sequence, worth testing in a clinical trial in view of the potential reduction in cardiotoxicity. Other agents: vinorelbine ± 5-fluorouracil (5-FU); cyclophosphamide, methotrexate, 5-FU (CMF); capecitabine; 5-FU c.i., continuous infusion; liposomal doxorubicin; gemcitabine. CT, chemotherapy; A, anthracycline; T, taxane; H, Herceptin® (trastuzumab).

in order to refine the prediction of response or resistance to trastuzumab and some groups have started looking at phosphorylated HER2 as a candidate for a more accurate prediction of outcome [9].

The next question that immediately follows identification of a suitable candidate for trastuzumab therapy is when and how should trastuzumab be given. The data gathered so far can be summarised by 'the earlier, the better'. The pivotal trial is particularly informative in this regard: it tells us that trastuzumab upfront is superior, in terms of survival, to trastuzumab as a 'salvage' treatment, since two thirds of patients in the control arm of this trial received trastuzumab at the time of progression. What we still do not know is whether trastuzumab 'upfront' needs to be given in combination with chemotherapy or whether it can be given, in selected patients, as monotherapy without compromising the chances of prolonged survival. In this latter scenario, patients would be spared the side-effects of chemotherapy for several months. With the recent report of substantial response rates to trastuzumab monotherapy given as first-line treatment for advanced breast cancer [10], this question becomes one of the highest priority questions to be addressed in a randomised clinical trial.

Last, but not least, another unanswered question at this moment is whether or not trastuzumab needs to be stopped at the time progressive disease is documented: indeed, one could argue that this 'biological' therapy has the potential of reducing the metastatic potential of HER2-overexpressing tumours, rendering them less 'aggressive' for as long as the treatment is continued.

Table 1
Pivotal trial of chemotherapy ± trastuzumab

Endpoints	HER-2 status	H + AC ($n = 143$)	AC ($n = 138$)	H + P ($n = 92$)	P ($n = 96$)	H + CT ($n = 235$)	CT ($n = 234$)
TTP (months)	2+	8.2	7.4	5.3	3.2	6.6	5.6
	3+	8.1	6.0	7.1	3.0	7.8	4.6
RR (%)	2+	40	45	21	10	32	34
	3+	60	42	49	17	56	31
DR (months)	2+	8.4	7.3	4.9	4.1	8.2	7.3
	3+	9.3	5.9	10.9	4.6	10.0	5.6
TTF (months)	2+	6.9	6.0	3.6	2.7	5.3	5.1
	3+	7.1	5.1	6.7	2.8	7.0	4.4
Survival (months)	2+	21	25	17	20	18	23
	3+	31	21	25	18	29	20

See Fig. 1 for T, H. TTP, time to progression; TTF, time to treatment failure; RR, response rate; AC, doxorubicin, cyclophosphamide; C, cyclophosphamide; P, paclitaxel; CT, chemotherapy; DR, duration of response.

Table 2
Response to trastuzumab monotherapy as a function of HER2 overexpression by immunohistochemistry (IHC)

IHC score	First-line treated patients		Heavily pretreated patients	
	n	%RR	*n*	%RR
HER2 2+	27	0	50	4
HER2 3+	87	35	172	17

RR, response rate.

Table 4
Response to trastuzumab monotherapy as a function of HER2 amplification by FISH

	First-line treated patients		Heavily pretreated patients	
	n	%RR	*n*	%RR
FISH−	21	5	37	0
FISH+	41	41	105	20

See previous tables for abbreviations.

Given the high costs associated with 'life-long' trastuzumab therapy, it is presently not recommended to continue trastuzumab beyond documented progression; in the meantime, a clinical trial addressing this important issue has been set up by the MD Anderson team (Fig. 2) and its results should become available in the next 2 years.

1.3. Chemotherapy

When chemotherapy is indicated, treatment options depend upon the type of previously administered adjuvant treatment. In the case of previous anthracycline exposure, the current best option appears to be the combination of trastuzumab with a taxane, with close monitoring of the left ventricular ejection fraction. Other trastuzumab-chemotherapy combinations, i.e. vinorelbine±trastuzumab; cyclophosphamide/methotrexate/5-fluorouracil (CMF)±trastuzumab, may also prove valuable and the results of ongoing and recently completed clinical trials of these and other combinations are eagerly awaited.

In the absence of prior anthracycline exposure, which is rare nowadays, the best treatment sequence remains to be defined, but could comprise the following:

1. Doxorubicin/cyclophosphamide (AC) followed, at progression, by a taxane plus trastuzumab, which mimics to a certain extent the pivotal phase III trial of chemotherapy±trastuzumab, but has the disadvantage of delaying trastuzumab treatment.
2. Taxane plus trastuzumab followed by anthracyclines later on in the disease course; this combination is worth exploring as a strategy that may maximise the survival benefit and that may be associated with a reduced cardiac risk.
3. In the event that data from recently closed phase III trials show anthracycline/taxane regimens to be associated with survival benefit compared with AC, the sequence doxrubicin/taxane (AT) followed by trastuzumab at the time of progression would need to be tested.

Table 3
Retesting of tissue slides FISH/IHC concordance [7]

		IHC			
		0	1+	2+	3+
FISH[a]	–	207	28	67	21
	+	7	2	21	176
		3%	7%	24%	89%

Overall concordance = 82%. FISH, fluorescent *in situ* hybridisation.
[a] FISH positivity highly concordant with substantial HER2 overexpression as determined by immunohistochemistry, IHC.

2. Adjuvant treatment options

It is felt that because of a lack of level 1, evidence-based studies demonstrating convincingly that tamoxifen is detrimental to HER2-positive patients, the use of tamoxifen in the presence of an ER/HER2-positive or PgR/HER2-positive tumour should not be overlooked. However, this is clearly a cause for concern and the issue is a high priority for clinical investigation.

HER2-positive patients who have contraindications for anthracycline-based chemotherapy should not be denied treatment with CMF. Despite this, anthracycline-based chemotherapy, with adequate doses of anthracyclines, appears to be today's best option outside the clinical trial setting.

Importantly, the relatively poor prognosis of HER2-positive patients together with the lack of information on the best use of trastuzumab in the adjuvant setting should motivate physicians to offer participation in prospective clinical trials in primary breast cancer. Such trials have started on the American continent and will be initiated soon in Europe. Their designs nicely com-

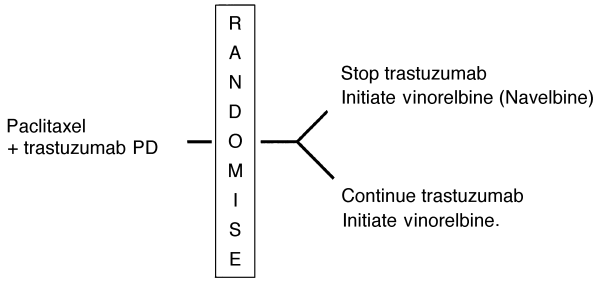

Fig. 2. The MD Anderson clinical trial investigating the issue of trastuzumab discontinuation at the time of progressive disease (PD).

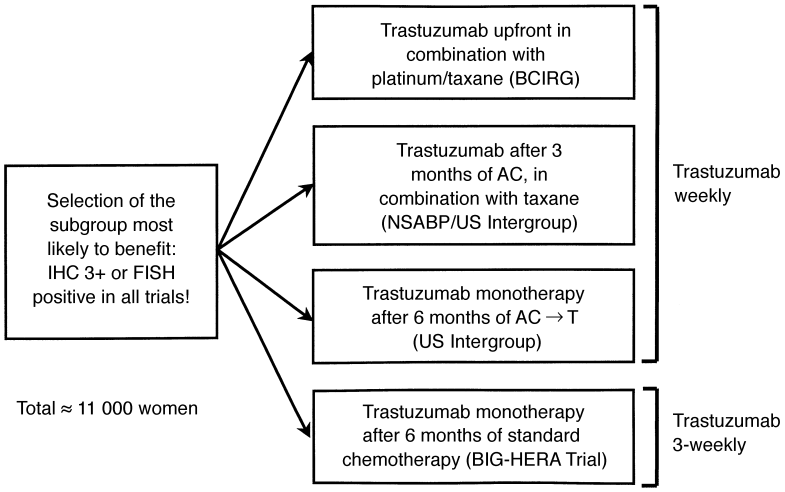

Fig. 3. Overview of trastuzumab adjuvant trial strategies.

plement each other (Fig. 3) with some trials exploring the value of *adding* trastuzumab to adjuvant chemotherapy while others investigate the value of trastuzumab given as a single agent after completion of adjuvant chemotherapy. Interestingly, the European trial will use a 3-weekly schedule of trastuzumab administration, based on encouraging pharmacodynamic/pharmacokinetic data generated by our Canadian colleagues [11].

Last but not least, *all* adjuvant trials are including a very close cardiac monitoring in the first few hundreds of patients enrolled.

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