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Review

Progress in systemic therapy for breast cancer: an overview and perspectives

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Abstract

This review will focus on progress for advanced and early breast cancer in systemic medical therapy, which consists of three main modalities: endocrine therapy (ET), chemotherapy (CT) and biological therapies (BTs). *In advanced disease*, we did witness two consecutive shifts in our classical sequence of ET: in the first one, the potent third-generation aromatase inhibitors took the second place after tamoxifen failure (a shift that is *level 1 evidence based*), making megestrol acetate a third option, while in the second, they are challenging tamoxifen as the 'gold standard' first line ET (a shift that is *level 2 evidence based*). As far as CT is concerned, most of the progress has been seen in anthracycline-resistant disease with the taxanes (docetaxel in particular) becoming the preferred treatment option on a *level 1 evidence* basis. In patients with no or limited anthracycline exposure, at least 10 randomised clinical trials involving the taxanes have been conducted, but in view of their conflicting results, no new standard of care has emerged. Third-line CT following anthracyclines and taxanes remains a wide-open research opportunity, with oral capecitabine being the only agent approved in this indication. Herceptin® (trastuzumab) is the first BTs available for the treatment of breast cancer. Its impressive clinical activity in metastatic breast cancer (MBC) prompted the registration of the drug for use as monotherapy in patients with HER-2 overexpressing MBC who have failed anthracyclines and taxanes, as well as for use upfront in combination with paclitaxel. There is substantial room for further progress with the use of Herceptin® in the management of breast cancer and much hope is placed in the combination of Herceptin® with other agents targeting important signaling pathways, such as the MAPKinase pathway or the PI_3 kinase cell survival pathway. Such strategies will be briefly discussed. In the area of *early breast cancer* management, BTs (namely Herceptin® and bisphosphonates) are being evaluated in randomised clinical trials, while ET has consolidated its prominent role for all women whose tumours express hormone receptors, as outlined in the 2000 NIH Consensus Conference and in the latest treatment guidelines proposed by the St-Gallen consensus panel in 2001. Substantial mutations in our standards of care are also expected in the field of adjuvant ET, with the early positive results of the large ATAC trial showing superior efficacy and tolerability of anastrozole over tamoxifen. The added benefits from adjuvant CT in patients receiving optimal ET remain difficult to ascertain and may be quite small in certain sub-groups. Only translational research efforts carry the hope for a much needed understanding of this complex interplay between ET and CT. With further improvement expected with new hormonal agents, it is possible that the role of CT will diminish in the future management of endocrine-responsive breast cancer, while the role of ET ± BTs will grow.

Keywords: Breast cancer; Review

1. Introduction

Progress in breast cancer rests on a multidisciplinary team effort involving basic researchers, radiologists, pathologists, surgeons, radiotherapists, medical oncologists, nurses, psychologists, etc. All these disciplines are currently evolving and contributing to improved management of women with breast cancer. Surgery, for example, is undergoing drastic changes with the implementation of sentinel lymphadenectomy, an elegant procedure likely to represent a major step forward with the avoidance of axillary dissection and its associated morbidity, in a majority of women showing no microscopic involvement of the sentinel nodes [1–6]. Radiotherapists are actively investigating new techniques with the aim to decrease the burden of treatment (e.g. intra-

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operative radiotherapy techniques [7–9], decrease the collateral irradiation of cardiac and pulmonary tissues (e.g. through 3-D-conformal radiotherapy or Intensity Modulated Radiation Therapy [10]) and improve its efficacy in patients at higher risk for a loco-regional recurrence [11].

This review will primarily focus on progress in systemic medical treatment, rather than having the ambition to cover all the other disciplines dealing with breast cancer management in a superficial way. There are three main modalities of effective systemic medical therapy for breast cancer: the oldest one is endocrine therapy (ET) that still is of utmost importance for patients whose tumours express estrogen and/or progesterone receptors, which account for about two-thirds of breast cancer patients; the least selective one is chemotherapy (CT) that may soon evolve from being based on relapse/progression risk-assessment to tailored administration according to the individual tumor pattern of gene expression; finally, the most rapidly expanding treatment modality is biological therapy (BTs), which includes approved drugs such as the bisphosphonates and the anti-HER-2 monoclonal antibody trastuzumab, and a growing list of new agents directed against molecular targets in the cancer cell and its environment the role of which is currently being evaluated. All systemic treatment modalities outlined above have been first explored in advanced breast cancer and subsequently transferred to early disease. For each setting, the 2002 'standards of care' that reflect the progress achieved in the last decade will be reviewed, and the prospects for improvement in the coming years will be discussed.

2. Advanced breast cancer

2.1. ET

We have been fortunate enough to witness a productive search for new hormonal agents in the last 10 years. While the data on novel antiestrogens are still maturing [12–19], the ones generated by the third-generation aromatase inhibitors (A.I.) have led to interesting 'mutations' in ET for breast cancer. Randomised clinical trials of A.I. run in postmenopausal women failing tamoxifen have enrolled no less than 4249 patients. Megestrol acetate was the comparator in five of these trials [20–24] and aminoglutethimide in two of them [25,26]. A superiority of the new A.I. has been shown in all trials in one or several endpoints, including overall survival (OS), time to progression (TTP), time to treatment failure (TTF), response rate (RR) or safety (Table 1). These highly consistent results across trials provided the *level 1 evidence* needed for a definite change in standard clinical practice and, indeed, third-generation A.I. (anastrozole, letrozole and exemestane) became the recommended second line ET following tamoxifen [27].

The next logical step was to move these new A.I. to first line ET, making a head to head comparison with tamoxifen: 2696 women who had had limited exposure to tamoxifen in the adjuvant setting were recruited into these trials. Pooled results of two similar double-blind trials have shown that anastrozole prolongs TTP in the subgroup of patients with known positive hormone receptors (HR) [28,29], and in a smaller, double-blind, phase II randomised trial, confined to women with HR-positive disease, an improved survival for anastrozole-treated patients was found [30]. Letrozole, however, showed striking superiority over tamoxifen in RR, TTP, TTF, and survival (up to 2 years) in a single, very large, randomised, double-blind trial, in which half of the patients did a crossover to the other agent at the time of disease progression, reflecting what is really happening in daily clinical practice [31,32]. Preliminary results from an open label, randomised phase II trial, comparing exemestane to tamoxifen looked very promising for the A.I., and prompted the extension of this trial into a phase III study that is still ongoing [33]. Taken together these first line data provide *level 2 evidence* that A.I. are to be preferred to our previous 'gold standard' agent, tamoxifen, and changes in standard clinical practice are likely to happen before the results of the exemestane trial become available, particularly in view of the excellent safety profile of these new endocrine agents. If indeed A.I. are becoming our preferred first-line ET in advanced breast cancer, what will be our most effective second-line treatment for women who are still considered 'endocrine responsive' and do not require immediate CT? This question remains unanswered! The fact that the survival curves in the letrozole/tamoxifen trial 'come together' after 2 years may suggest a relatively poor 'performance' of tamoxifen, when given following letrozole; in any event, these data point to the need of additional clinical research aiming at more effective 'salvage' therapies after A.I. failure. These salvage therapies are particularly important in view of the likelihood that A.I. will soon be incorporated in adjuvant therapy for early breast cancer (discussed below). Potential candidates are newer antiestrogens, such as Faslodex®, which has already demonstrated equivalence to anastrozole in tamoxifen failures [34,35], and biological agents (e.g. Iressa®) that may delay or prevent the onset of hormone resistance.

2.2. Chemotherapy

Two major actors have occupied the front scene in the last decade: paclitaxel and docetaxel. These anti-microtubule agents, with their innovative mechanism of action that is *p-53*-independent [36–39], have been the subjects of numerous clinical trials either as single

Table 1
Randomised trials of third-generation aromatase inhibitors as second-line hormonal therapy in metastatic breast cancer

Study	Design	Population	No pts	Endpt	AI	Std	*P*-value	Toxicity
Buzdar, Jonat and pooled results[a] [20]	Anastrozole 1 mg/d or 10 mg/d versus MA 160 mg/d	US study (6 m follow-up)	386	RR	10/6%	6%	NS	A.I: GI side-effects
				CB	37/30%	36%	NS	MA: wt gain
		European study	378	CB	34/34%	33%	NS	A.I.: GI side-effects MA: wt gain, edema, dyspnoea
		Pooled data	764	RR	10/9%	8%	NS	A.I.: GI side-effects
		Post,		CB	35/32%	34%	NS	MA: wt gain
		TAM failure		OS	26.7 m	22.5 m	0.025	
Dombernowsky [21]	Letrozole 0.5 mg/d or 2.5 mg/d versus MA 160 mg/d	TAM failure	551	RR	12/24%	16%	0.004	Thromboembolic events:
							(2,5 mg/d)	A.I. 5 mg = 2; AI 2.5 mg = 0
				TTP	5.1/5.6 m	5.5 m	0.07	MA = 15
Goss [22]	Vorozole 2.5 mg OD versus MA 40 mg gid	TAM failure	452	RR	19.7%	7%	N/A	MA: wt gain, dyspnoea
		MBC 2nd line		CB	23.50%	27%	NS	A.I: nausea, hot flashes, anorexia
				DR	18.2 m	12.5 m	0.07	
Kaufmann[a] [23]	Exemestane 25 mg OD versus MA 160 mg/d	TAM failure	769	RR	15%	12%	NS	A.I: >5%: *n*, hot flashes, fatigue
		MBC		TTP	4.7 m	3.8 m	0.04	MA: >5%: fatigue, sweating, appetite, nausea, hot flashes
				OS	Not reached	28.4m	0.04	
Buzdar [24]	Letrozole 0.5 mg/d or 2.5 mg/d versus MA 160 mg/d	TAM failure	602	RR	21% /16%	15%	*NS*	MA: wt gain, dyspnea, vaginal bleeding. A.I: headache, hair thinning, diarrhoea
				TTP	6 m/3 m	3 m	*NS*	
				TTF	5 m/3 m	3 m	*0.018*[b]	
				TTD	33 m/29 m	26 m	*0.053*[b]	
Bergh [25]	Vorozole 2,5 mg/d versus AG 250 mg/bid	TAM failure	556	RR	23%	18%	NS	Tolerability score: 0.4 versus 0.7
		MBC 2nd line		CB	47%	37%	0.017	(⩽0.001)
				TTP	6.7 m	6.0 m	NS	% AE: 31% versus 53% (<0.001)
				TTF	5.3 m	4.4 m	0.040	% Drop outs: 3% versus 10%
				OS	25.7 m	21.7 m	NS	(<0.001)
Gershanovich [26]	Letrozole 0.5 mg or 2.5 mg versus AG 500 mg/d	TAM failure (1st/2nd line MBC)	555	RR	17/20%	12%	NS	Letrozole: nausea
				DR	21/24 m	15 m	Trend	AG: rash
				OS	21/28 m	20 m	0.0002	

NS, not significant; MA, megestrol acetate; Std, standard treatment; wt, weight; post, postmenopausal; VTE, venous thromboembolic disease; GI, gastrointestinal; Endpt, endpoint; m, months; AE, adverse events; TTD, Time to death; TTP, time to progression; TTF, time to treatment failure.

[a] Significantly better OS for AI (For anastrozole 1 mg, only pooled studies showed OS advantage). None of these trials examined OS as primary endpoints.

[b] *P* values regarding comparison between Letrozole dose of 0.5 mg/d and MA; differences not significant for dose level of 2.5 mg/d.

Table 2
Randomized phase III trials of taxanes in metastatic breast cancer

Study	Population	No. pts	Compared treatments	RR (*P* value)	TTP (*P* value)	OS (*P* value)	Crossover
Single agent							
Nabholtz [40]	Anthracycline resistant	392	Docetaxel	30.0%	19 ws	11.4 ms	Allowed. 12 and 24%, respectively.
			Mitomycin + vinblastine	11.6% (<0.0001)	11 ws (0.001)	8.7 ms (0.0097)	
Sjostrom [41]	Anthracycline resistant	283	Docetaxel	42%	6.3 ms	10.4 ms	Recommended.
			Methotrexate → 5-FU	21% (<0.001)	3.0 ms (<0.001)	11.1 ms (0.79)	18 and 28%, respectively.
Chan [47]	Prior alkylating agents	Total: 326	Docetaxel	47.8%	26 ws	15 ms	Allowed.
		2nd line: 174	Doxorubicin	33.3% (0.008)	21 ws	14 ms	28 and 26%, respectively.
Monnier [42]	Anthracycline resistant	172	Docetaxel	33%	6.0 ms	NA	NA
			Vinorelbine + 5-FU	26%	5.0 ms		
Bishop [44]	1st line	209	Paclitaxel	29%	5.3 ms	17.3 ms	No crossover. At progression pts were recommended to receive Epirubicin
			CMF-pred	35% (0.37)	6.4 ms (0.25)	13.9 ms (0.068)	
Paridaens [45]	1st line	331	Paclitaxel	25%	4.2 ms	15.6 ms	Early (76 *vs* 75%) and delayed (46 *vs* 65%) crossover part of the study design
			Doxorubicin	41% (0.003)	7.5 ms (<0.001)	18.3 ms (0.38)	
Combination							
Sledge [46]	1st line		Paclitaxel	33%	5.9 ms	20.1 ms	Allowed but not part of study design
		739	Doxorubicin	34%	6.2 ms	22.2 ms	
			Paclitaxel + doxorubicin	46% (<0.007)	8.0 ms (<0.009)	22.4 ms	
Jassem [54]	1st line	267	Paclitaxel + doxorubicin	68%	8.3 ms	23.3 ms	Not part of the design but 10% of pts in the FAC arm received paclitaxel as 2nd line
	Anthrac naïve	FAC	55% (0.032)	6.2 ms (0.034)	18.3 ms (0.013)		
Nabholtz [48]	1st line	429	Docetaxel + doxorubicin	60%	37.1 ws	NA	NA
	Anthrac naïve		Doxorubicin + cyclophos phamide	47% (0.012)	31.9 ws (0.015)		
Nabholtz [53]	1st line	484	TAC	54%	37.3 ws	NA	NA
			FAC	43% (0.023)	31.9 ws (0.014)		
Luck [49]	1st line	429	Paclitaxel + epirubicin	46%	39 ws	NA	NA
			Epirubicin + cyclophos phamide	41%	33 ws (0.089)		
Biganzoli [51]	1st line	275	Paclitaxel + doxorubicin	58%	5.9 m	20.6 m	Allowed but not part of study design
	Anthrac naïve		Doxorubicin + cyclophos phamide	54% (0.51)	6.0 m (0.69)	20.5 m	
Carmichael [52]	1st line	705	Paclitaxel + epirubicin	67%	6.5 m	13.7 m	NA
			Epirubicin + cyclophos	56%	6.7 m (0.72)	13.8 m (0.92)	

(*continued on next page*)

Table 2 (*continued*)

Study	Population	No. pts	Compared treatments	RR (*P* value)	TTP (*P* value)	OS (*P* value)	Crossover
Single agent versus combination							
Leonard [43]	Anthracycline resistant	511 ⩾ 2nd line: 340	Docetaxel + capecitabine	41.60%	6.1	14.5	Not part of study design; only 15% of women on the docetaxel arm received capecitabine
			versus Docetaxel	versus 29.7%* (0.006)	versus 4.2 ms* (0.0001)	versus 11.5 ms* (0.0126)	

TAC, docetaxel + doxorubicin + cyclophosphamide; FAC, 5-FU + doxorubicin + cyclophosphamide; m, months; ws = weeks; NA, not available.

agents or in combination with other cytotoxic compounds. From the randomised trials, it appears that the taxane with the best documented activity in anthracycline-pretreated or resistant patients is docetaxel (Table 2): as a single agent, docetaxel was found to be superior to two commonly used combinations (mitomycin + vinblastine and methotrexate + 5-fluorouracil (5-FU)) [40,41] and as effective and better tolerated than a third one (vinorelbine + 5-FU) [42]. Its combination with the new antimetabolite capecitabine led to superior results over its single agent use in a similar patient population [43]. In patients with minimal or no prior exposure to anthracyclines, paclitaxel surpassed CMFPrednisone in one trial [44] but generated conflicting results when compared to doxorubicin, with inferiority in one trial [45] and equivalence in another [46]. Docetaxel was shown to induce more responses than doxorubicin in a single trial [47]. The next logical development was to combine taxanes with anthracyclines. Unfortunately, these new regimens have not consistently shown superiority over non-taxane regimens [46,48–54] and improvement in survival has been reported, so far, in only one trial [54]. These data would clearly benefit from a meta-analysis that could not only disclose a small but real survival gain not detected in the individual trials (which involved each less than 500 patients) but also identify potential subgroups of patients likely to derive the greatest benefit from a taxane-anthracycline combination. In the meantime, taxanes have become a new standard of care in anthracycline-resistant disease and are preferred to other options in women with life threatening metastases. Nevertheless, no consensus exists as to their preferential use as single agents or in combination.

The true impact of CT on survival and quality of life of MBC patients is still debated and under evaluation, especially for second and subsequent lines of treatment. These are consistently associated with fewer responses and no discernible or no consistent effect on median survival, and, so far, no 'standard regimen' has emerged as second-line CT for MBC [55]. One particularly difficult sub-group, for which the randomised evidence is scant, is women pretreated or resistant to both anthracyclines and taxanes. In this setting, capecitabine is the drug with the best documented phase II activity and a randomised EORTC trial will soon start comparing this new oral fluoropyrimidine to the older drug vinorelbine.

A number of newer cytotoxic agents are under clinical evaluation in MBC, such as the multitargeted antifolate Alimta [56–58] and the epothilones, a new promising class of antitubulin agents that seem to lack cross-resistance with taxanes in preclinical models [59–63]. These agents are unlikely to lead to a dramatic progress in the treatment of advanced breast cancer but, if the taxanes move to the adjuvant setting in the next 2–4 years, there will be an urgent need for active and non cross-resistant

cytotoxic agents, for all women experiencing an early relapse following adjuvant CT.

2.3. Biological therapies (Table 3)

The only BTs currently approved for the treatment of advanced breast cancer are trastuzumab (Herceptin®), a humanised monoclonal antibody (Mab) produced against the extracellular domain of *HER-2*, a type 1 tyrosine kinase receptor of the HER family, and the bisphosphonates clodronate and pamidronate. Since the cloning of the human *HER-2* gene in 1985 and the identification of its corresponding protein Her-2, the following sequence of events took place: (1) the correlation between *HER-2* gene amplification and/or Her-2 receptor overexpression with an aggressive form of breast cancer, (2) the demonstration that the murine Mab 4D5 markedly inhibits the proliferation of human tumour cells overexpressing Her-2, (3) the humanisation of 4D5 to produce the drug Herceptin®, (4) the initiation of clinical trials in 1992, (5) the registration of the drug worldwide for use as monotherapy in patients with HER-2 amplified/overexpressing MBC, who have failed anthracyclines and taxanes, as well as up-front use in combination with paclitaxel, between 1998 and 2000, and (6) the initiation of large adjuvant randomised clinical trials on both sides of the Atlantic ocean in 2000–2001. Further progress with the use of trastuzumab in the management of breast cancer is likely to occur in the following areas: (1) optimisation and standardisation of HER-2 testing, which is currently based on different immunohistochemistry procedures, namely with different antibodies, and/or fluorescence *in situ* hybridisation (FISH), with great concern regarding the lack of interlaboratory reproducibility [64,65]; (2) the refinement of the administration schedule of trastuzumab, which was recently found to have a much prolonged half-life, in the range of 28 days, an observation that prompted the investigation of a 3-weekly regimen, as opposed to the current weekly administration [66,67]; (3) the elucidation of the mechanisms of resistance to trastuzumab, given that close to two-thirds of women with HER-2 amplified/overexpressing breast cancer do not experience objective responses, and that the median duration of response to this drug is around 9 months; (4) the identification of predictive factors for its potential cardiotoxicity; (5) the understanding of the relative merits of up-front single-agent trastuzumab versus combination with CT, in terms of survival and quality of life; and (6) the exploration of combinations of trastuzumab with other targeted therapies (see below).

The successful development of trastuzumab gives the hope that other targeted therapies will soon become available and enhance the ability to control systemic disease. Multiple new targets for anticancer therapy have been identified in a variety of molecular pathways relevant to the biology of the breast cancer cell: these include the signal transduction pathway, cell-cycle control, the apoptotic pathway and the angiogenesis/metastases pathway. Beyond target identification, which has become easier in this era of genomics and proteomics, there is a task of target 'credentialling'

Table 3
Some new biological agents with clinical potential in breast cancer treatment

Agent	Class	Target	Current status of clinical development in breast cancer
Trastuzumab (Herceptin®)	Monoclonal antibody	Her-2	Registered for use in MBC worldwide
			Phase III trials in the adjuvant setting ongoing
Tak 165	Tyrosine kinase inhibitor	Her-2	Starting phase I evaluation
ZD1839 (Iressa®)	Tyrosine kinase inhibitor	EGFR	Starting phase II evaluation
OSI-779 (Tarceva®)	Tyrosine kinase inhibitor	EGFR	Starting phase II evaluation
CI-1033	Tyrosine kinase inhibitor	Pan-HER	Finishing phase I evaluation
R-115777 (Zarnestra®)	RAS farnesyl transferase inhibitor	RAS and other farnesylated proteins	Activity seen in single-agent phase II trials
			Starting phase III trials
BAY 43-9006	RAF kinase inhibitor	RAF	Finishing phase I evaluation
ZD6474	Tyrosine kinase inhibitor	VEGFR	Finishing phase I evaluation
RhuMAB VEGF	Monoclonal antibody	VEGF	Modest activity seen in phase II trials
SU6668	Tyrosine kinase inhibitor	VEGFR, PDGFR and FGFR	Finishing phase I evaluation
CCI-779	m-TOR inhibitor	m-TOR (PI3 kinase survival pathway)	Responses seen in single-agent phase I trials
			Finishing single-agent phase II evaluation
			Starting phase I/II combination trials
PS-341	Proteasome inhibitor	Proteasome	Activity seen in single-agent phase I and II trials
			Phase I combination trials ongoing

MBC, metastatic breast cancer.

followed by 'target validation' through properly designed and conducted clinical trials. Other promising candidate receptors for this challenging development process include, in the cancer cell, the epidermal growth factor receptor (EGFR, also known as HER-1) and, in the stromal cell, the vascular endothelial growth factor receptor (VEGFR), the fibroblastic growth factor receptor (FGFR) and the platelet-derived growth factor receptor (PDGFR). An impressive list of new drugs targeting these receptors is currently under several phases of clinical development— these include monoclonal antibodies (e.g. Cetuximab or C225, directed against the EGFR), small molecules tyrosine kinase inhibitors (e.g. Iressa or ZD1839 and OSI-779, directed against EGFR tyrosine kinase; or ZD6474 and SU5416 against VEGFR), antisense oligonucleotides (e.g. anti mRNA of bcl2), and immunoconjugates (e.g. ScFv(225) or (14E1) ETA). Interestingly, some of these new agents target two or more receptors of the HER family simultaneously, such as CI-1033 and PKI116, which inhibit both EGFR and HER-2, PD 158780 that blocks EGFR, HER-2 and HER-4, or, in the angiogenesis/metastases pathway, SU6668 that targets VEGFR, PDGFR and FGFR. None of these antireceptor agents has completed phase III evaluation and, therefore, their future role in breast cancer management remains speculative. The same remark applies to a number of innovative antisignal transduction agents that have a target located downstream of the cell surface membrane receptor. One such agent, R-115777 or Zarnestra®, is a farnesyltransferase inhibitor with oral bioavailability that has shown modest single-agent phase II activity in advanced breast cancer [68], as well as a favourable safety profile, allowing its combination with cytotoxic agents such as docetaxel or with trastuzumab [69,70]. Another new agent with a promising clinical potential in breast cancer is CCI-779 that inhibits mTOR, an important mediator in the PI3 kinase survival pathway: a single-agent phase II trial is ongoing and combination phase I/II studies are being planned.

Bisphosphonates are an integral part of the treatment of women with lytic bone metastases and are most often used in combination with ET or CT. This new standard of care is the result of well-conducted, placebo-controlled randomised clinical trials that have clearly shown reduced skeletal morbidity in women receiving those powerful anti-osteoclastic drugs. The bisphosphonate family continues to grow and the new generation compounds, in view of their increased potency, are expected to be even more efficacious and more convenient to use [71–73].

2.4. Combined modality therapy

2.4.1. Combined endocrine therapy and chemotherapy

This is not recommended in advanced breast cancer based on the lack of a demonstrable survival improvement associated with this strategy in 19 trials conducted between 1977 and 1996 (trials reviewed in Ref. [74]. Of note, all these trials were small, underpowered and none included a third-generation aromatase inhibitor or Faslodex®. It would be interesting to re-explore this concept, using more active hormonal agents and improved trial designs.

2.4.2. Combined chemotherapy and biological therapies

This is a promising strategy that has the potential to increase the rate as well as the duration of objective tumor regressions. An elegant 'proof of concept' was provided by the pivotal trial of CT ± trastuzumab in MBC [75], and it is hoped that similar encouraging results will be obtained with other biological agents.

2.4.3. Combined endocrine and biological therapies

This is another attractive strategy that could delay the onset of hormone-resistance through the use of new biologic agents targeting signaling pathways important for the survival of the endocrine-resistant breast cancer cell. Interesting preclinical studies performed in the United Kingdom nicely showed a switch towards EGFR signalling pathway and a gain in sensitivity to Iressa® at the time hormone-sensitive breast cancer becomes hormone-resistant [76]. These observations form the rationale of a soon-to-start European Organisation for Research and Treatment of Cancer (EORTC) trial in which patients failing tamoxifen will be randomised to anastrozole + Iressa® or anastrozole + placebo.

2.4.4. Combined biological therapies

In view of the well-known heterogeneity of solid tumours and the redundancy of survival pathways in the cancer cell, it is tempting to speculate that progress will emerge from the combined use of several 'targeted' therapies. These new combinations will have to be based on a solid scientific or preclinical rationale, since they will drastically increase the costs of new drug development, and consequently the costs of healthcare. One such combination, which is starting to be evaluated in breast cancer, is the combination of Herceptin® with the proteasome inhibitor PS-341. PS-341 belongs to a new and promising class of anticancer agents, the proteasome inhibitors, which target the proteasome, a multiprotease complex responsible for the degradation of various proteins, including membrane receptors [77,78]. It has demonstrated antitumour activity in breast cancer *per se*, both in preclinical and clinical studies [79]. Since the proteasome has been implicated in the HER-2 protein degradation pathway, it is foreseeable that, by inhibiting its action, the number of available HER-2-receptors could be increased [80,81] and, hence, Herceptin®'s efficacy. Other potential mechanisms of synergy between the two molecules are through their effects on NFkB and p27 [82,83].

2.5. Supportive therapy

2.5.1. Erythropoietin

There is increasing awareness in the oncology community about the important contribution of anaemia to the common problem of 'fatigue' in cancer patients, as well as its potential negative impact on the efficacy of radiotherapy and CT [84–88]. The hypothesis that anaemia needs to be corrected early on in MBC patients receiving first-line CT, in order to optimise its efficacy, has been tested in a prospective randomised clinical trial in which half of these women received erythropoietine at the first signs of anaemia (fall of hemoglobin below 12 g/dl), while the other half received red blood cell transfusions in case of symptomatic anaemia. Results of this trial, which has survival as the primary endpoint, should be available in the near future.

2.5.2. Pegylated G-CSF

Haematopoetic growth factors of the white cell lineage are recommended as secondary prophylaxis in cancer patients who develop febrile neutropaenia under cytotoxic treatment or as primary prophylaxis in case the cytotoxic regimen used is associated with a rate of febrile neutropaenia in the range of 30–40% [89]. Pegylated filgrastim recently showed equivalent efficacy in comparison with daily filgrastim, and greater convenience to patients and healthcare providers given its one per cycle administration [90,91], and the process of its regulatory approval is ongoing both in the US and in Europe. Of note, the pivotal registration trial was conducted in advanced breast cancer patients treated with the highly myelosuppressive doxorubicin–docetaxel combination.

3. Early breast cancer

Systemic therapy for early breast cancer (EBC) is of utmost importance since it has a curative potential and therefore may decrease breast cancer mortality. Two challenging tasks for the medical oncologist, here are: first, a proper evaluation of the patient's risk of relapse, and, second, the selection of the most appropriate systemic therapy, if indeed systemic therapy is indicated on the basis of recurrence risk.

3.1. Evaluation of the risk of relapse

In spite of huge progress in our biological understanding of breast cancer, risk classification of early disease continues to rest on traditional prognostic factors which, according to the most recent consensus conferences, include nodal status, tumour size, tumour grade, age and hormone-receptor status [92,93]. There is little doubt that this situation will change dramatically in the next decade as a result of accelerated progress in proteogenomics. There are early encouraging signs that dissection of the tumour genetic profile with correlation to patient outcome will markedly improve our ability to predict which patients are going to experience a relapse, and which patients are cured of their first breast cancer by locoregional therapy. This is particularly important in an era of widespread use of screening mammography that markedly increases the proportion of small invasive cancers with a relatively low-risk spectrum. The work of the Amsterdam group is particularly impressive: with the use of microarray technology, these investigators were able to identify a limited number of genes that predict the 8-year relapse-free survival in a series of 97 untreated women with node-negative breast cancer [94]. This 'genetic signature' is now being validated in another series of 300 node-negative breast cancer patients.

3.2. Selection of the most appropriate form of adjuvant therapy

The work of the Early Breast Cancer Trialist Group has been instrumental in our understanding of which therapies do provide a sustained survival benefit, and what is the magnitude of this benefit on average [95,96]. Our three main adjuvant treatment modalities in 2002—namely, tamoxifen, ovarian ablation and CT—all provide absolute survival gains ranging between 2 and 12% at 10 years of follow-up. While we no longer worry about the effectiveness of these therapies, we are still struggling with: (1) the choice of the optimal CT regimen, particularly in endocrine non-responsive disease (i.e. when the tumour is devoid of oestrogen and progesterone receptors); (2) the choice of the optimal ET for endocrine-responsive disease; and (3) the decision when to offer combined modality therapy (i.e. ET + CT).

3.3. Optimal adjuvant chemotherapy in 2002

Anthracyclines and taxanes are considered the most active cytotoxic agents against breast cancer.

The value of anthracyclines in the adjuvant setting has long been evaluated, but only recently was their superiority over CMF regimens established beyond any doubt. However, this superiority is less impressive than expected, on average not exceeding a 4% absolute gain in 10-year survival for node-positive disease and a 1.7% gain at 5 years for node-negative diseases [96]. Furthermore, these benefits must be balanced against increased short and long-term toxicity, and the magnitude of the absolute benefit is a function of the underlying risk, which depends on patient and tumour characteristics. These findings highlight the need for reliable predictive factors that may enable the clinician to individualise the treatment choice for each patient. For node-positive breast cancer patients, independently of the number of

nodes involved, anthracyclines are currently considered the first treatment option, while CMF is used only if there are clear contra-indications for the use of anthracyclines. This is a level 1 evidence-based conclusion and both the National Institutes of Health (NIH) and the St Gallen consensus panels [92,93] support it. Of interest, the advantage of anthracycline-based CT was found almost exclusively when a three-drug regimen was used (either CEF or CAF), while four cycles of a two-drug regimen (e.g. AC) seem to be equivalent to six cycles of CMF (studies reviewed in Ref. [97]). A direct comparison between four cycles of AC and six cycles of CEF will help resolving the controversy and is considered by the NSABP group.

The role of taxanes in the adjuvant setting is still under evaluation. So far, four randomised trials have been reported, all of which evaluate the role of adding a taxane to an anthracycline-based regimen, and in only three of them are results of DFS and OS available. The preliminary results of the CALGB 9344 trial showed superior outcome for the paclitaxel arm in terms of DFS and OS, particularly in the sub-group of patients with ER-negative tumours; in the update at 52 months of follow-up, the difference in OS is no longer significant and the relative decrease in the risk of recurrence, while still statistically significant, dropped by almost half [98–100]; however, in the most recent update of this trial, a survival gain has once more emerged for the paclitaxel-containing arm ($p = 0.01$). Two other studies, the M.D. Anderson trial and the NSABP-B28 trial, failed to show a benefit from adding paclitaxel to a FAC or AC regimen [101,102]. Preliminary results of the NSABP-B27 trial were recently presented, showing a higher rate of clinical and, more importantly, pathological complete responses, with the use of four cycles of AC followed by four cycles of docetaxel, both given in the neoadjuvant setting as opposed to AC alone or in combination with post operative docetaxel [103]; although these results are encouraging, they must be interpreted with caution, since no results on DFS or on OS were presented so far. Furthermore, this trial, the CALGB 9344 and NSABP-B28 trials share the same design limitations, namely the use of a non-consensual 'standard' regimen and a difference of 12 weeks in the duration of CT treatment between the arms, which is a potential confounding factor.

In summary, the available results are still inconclusive and do not support the routine use of taxanes in the adjuvant setting. However, several large randomised clinical trials, comparing taxane-based regimens to anthracycline-based ones and to the combination of both agents, either concurrently or sequentially, are currently ongoing or have recently closed accrual. These trials will recruit more than 17 000 women, and it is anticipated that they will provide a definitive answer regarding the role of taxanes in the adjuvant treatment of breast cancer, within the next 5 years [97,104].

3.4. Optimal adjuvant endocrine therapy in 2002

Until the end of 2001, tamoxifen has remained the gold standard adjuvant ET for postmenopausal women, with a 20-year learning curve regarding its optimal use (5 years of treatment or possibly more), its side-effect profile (with thromboembolic disease and uterine cancer as rare but potentially life-threatening complications) and its 'chemoprevention effect' on the contralateral breast (with a halving in the occurrence of second primary breast cancers). The recent presentation of the early results of the large ATAC trial (anastrozole, tamoxifen and the combination of both in postmenopausal women with breast cancer) is challenging this 'standard of care': at a median treatment duration of 2.5 years, anastrozole demonstrates superior efficacy and tolerability over tamoxifen, while no advantage is seen for the combination. More specifically, anastrozole decreases the hazard ratio of relapse by 17%, and the risk of contralateral breast cancer by 58%; it is better tolerated with respect to endometrial cancer, vaginal bleeding, vaginal discharge, ischaemic cardiovascular events, venous thromboembolic events, hot flushes and weight gain, while tamoxifen retains a small advantage as far as musculoskeletal disorders and fractures. Although a complete risk/benefit analysis must await a longer follow-up, with particular attention paid to bone mineral density and cognitive function, these early results are provocative and point to the great potential of third-generation aromatase inhibitors in the adjuvant as well as in the chemoprevention setting [105]. It should be emphasised that this superiority was not, however, seen in the 20% of patients who also had prior adjuvant chemotherapy.

In young premenopausal patients whose tumours contain hormone receptors, recent alarming data show that CT performs poorly as a single-treatment modality, suggesting the important contribution of some form of ovarian ablation (which rarely occurs in those young women with CT alone) to outcome [106]. At the same time, a series of randomised clinical trials, that have made head to head comparisons between ovarian ablation (±tamoxifen) and CT, have shaken our belief that CT is *the* superior treatment modality for premenopausal women having endocrine-responsive breast cancer [107–112]. While these trials do not represent definitive evidence that ovarian ablation can replace CT, in view of their sub-optimal designs and modest sample sizes, they point to the need to carefully re-evaluate the respective merits of each treatment modality, alone and in combination, in selected sub-populations. Finally, a series of trials are trying to characterise the benefit/risk ratio associated with tamoxifen, ovarian

ablation or both in premenopausal women with hormonal receptor-positive breast cancer [113].

3.5. Combined endocrine therapy and chemotherapy

As we become aware of the important contribution of 'optimal adjuvant ET' to improved survival of endocrine-responsive breast cancer, the additional benefit of CT needs to be carefully reassessed. There are indeed low risk sub-groups for which this additional benefit, if it is exists, might be of small magnitude, and might not justify the associated short-term and long-term side-effects. In premenopausal women with hormonal receptor-positive breast cancer, two complementary clinical trials will soon be initiated by the International Breast Cancer Study Group (IBCSG). The first will evaluate the benefit of ovarian ablation, given in addition to tamoxifen, in young women who retain their menses at completion of adjuvant CT. The second is the mirror image of the first and will assess the potential merits of CT given in addition to ovarian ablation + tamoxifen in a sub-group of premenopausal women for which ET has been selected as the primary adjuvant systemic treatment.

3.6. The contribution of predictive markers to the selection of systemic therapy

Hormone receptors (both ER and PgR) expression for adjuvant endocrine therapy and HER-2 overexpression for Herceptin®'s activity are the only predictive markers with a level I evidence that justifies routine use in current clinical practice. Nevertheless, about one-third of ER and/or PgR positive tumours and two-thirds of *HER-2*-positive breast cancers do not respond to ET and to trastuzumab, respectively. These facts clearly indicate the need for additional predictive markers, which are also badly needed for tailoring CT regimens.

In recent years, the most extensively studied biological marker has been the *HER-2* proto-oncogene and its protein. Although preclinical data suggested that HER-2 overexpression could be associated to decreased efficacy of tamoxifen and even to a potential detrimental effect [114,115], clinical studies, both in the metastatic and the adjuvant setting, addressed this issue and provided contradictory results. Therefore, the current recommendation is that tamoxifen should not be withheld from patients with ER and/or PgR-positive tumours, solely on the basis of HER-2 overexpression. Preliminary data, that need confirmation, suggest a much improved activity of third-generation A.I. as compared to tamoxifen, in patients whose tumours co-express ER and/or PgR and HER-2 and EGFR [116]. Overexpression of Bcl-2 has been associated with a greater benefit from adjuvant tamoxifen [117,118]. Other potential predictive markers of hormone responsiveness, such as the β isotype of ER, *p53* mutations, the proliferation marker Ki67, and intratumoral aromatase activity (for aromatase inhibitors) are under evaluation.

With regard to CT, a growing number of factors are being evaluated as potential predictive markers to help with the selection of the best regimen. However, due to the lack of prospective studies and technical difficulties, namely the reproducibility of the assessment methods across different laboratories, no predictive marker is so far recommended for routine use in clinical practice [92,93]. Among the studied markers, HER-2 is the one where the largest volume of data has been gathered: HER-2 amplification/overexpression has been associated with a higher probability of response to anthracycline and taxane-based CT, and with some degree of resistance to CMF and CMF-like regimens ([119], studies reviewed in Ref. [120]). Regarding anthracycline-based CT, a new and promising predictive marker, topoisomerase II alpha (topo II-α) has recently drawn researchers attention. Since this enzyme is the main target of anthracyclines, its overexpression may render the cells more sensitive to these agents. Moreover, preclinical data has shown that *topo II-α* amplification only occurs with concurrent *HER-2* amplification; therefore, it is possible that the predictive value of *HER-2*, regarding anthracycline-based CT, is explained by the concomitant amplification of the *topo II* gene [121–124]. For taxane-based regimens, the most attractive markers are the microtubule-associated parameters (MTAP), which are a specific target for these drugs. The *Tau* gene and the class II β-tubulin isotype have yielded promising results in a pilot study [125] but confirmation of these results is warranted. *P53*-mutated tumours appear to have a high response rate when treated with taxanes and a low response rate when treated with anthracyclines [126–128]. To confirm this hypothesis, a large multicentric international prospective trial has recently begun, under the auspices of the Breast International Group (B.I.G.) and coordinated by EORTC [104]. Lastly, evidence from colorectal cancer studies suggests that tumours with low levels of thymidilate synthase (TS), the target enzyme of 5-FU, are more responsive to 5-FU-based therapies than tumours with high TS levels. Furthermore, the ratio of TS to dihydropyridine dehydrogenase (DPD), which metabolises 5-FU to an inactive molecule, may also be predictive of response to 5-FU. Evaluation of TS and DPD levels in advanced breast cancer may identify patients most likely to benefit from the fluoropyrimidines [129,130].

With the initiation of prospective randomised trials, indispensable for the clinical validation of all these putative predictive factors, and with the implementation of the micro-array technique, the effort devoted to translational research will continue to expand and contribute to improved treatment tailoring as well as to a better

understanding of the biology of cancer, with the identification of relevant targets for new anticancer agents.

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