Preoperative endocrine therapy for breast cancer

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Abstract

The preoperative use of systemic therapy for primary breast cancer has the potential to downstage tumours. This would render suitable for breast conservation some tumours that were unsuitable at initial presentation, or would convert some inoperable locally advanced breast cancers into tumours that are operable. No survival benefit has been demonstrated for neoadjuvant chemotherapy compared with the same therapy given in an adjuvant setting. Preoperative endocrine therapy, in contrast to neoadjuvant chemotherapy, has fewer side effects and has the potential additional advantage that it can be continued throughout the perioperative period. Current data have shown that, in patients with an oestrogen receptor (ER)-positive tumour, a response approaching 70% could be reached in approximately 3 months using traditional endocrine manipulation such as tamoxifen. Randomised clinical trials are warranted to demonstrate the superiority of preoperative endocrine therapy over conventional adjuvant endocrine therapy, to define the optimum duration of therapy, and to identify the best endocrine agents. Both clinical and laboratory studies are also required to identify factors (in addition to ER) that would precisely predict the response and hence to select appropriate patients and to improve existing methods of monitoring response.

Introduction

The use of adjuvant systemic therapies has been shown to improve survival of patients with primary breast cancer and, specifically, the role of endocrine therapy in this situation is well established (Scottish Cancer Trials Breast Group and ICRF Breast Unit, Guy’s Hospital, London 1993, Early Breast Cancer Trialists’ Collaborative Group 1998). Traditionally adjuvant systemic therapy is instituted after completion of primary locoregional treatment, which is usually in the form of surgery with or without radiotherapy. Knowing that, in a large proportion of patients, breast cancer is a systemic disease at presentation, it seems reasonable to consider preoperative systemic therapy. Both phase II and randomised phase III trials of neoadjuvant chemotherapy have been reported, but the preoperative use of endocrine therapy in women with primary breast cancer has not been widely investigated.

Randomised studies of neoadjuvant chemotherapy (Powles et al. 1995, Fisher et al. 1997, 1998) have shown no survival benefit of the technique, but have confirmed that, in a proportion of patients, neoadjuvant chemotherapy can be used to downstage large primary breast cancers. However, experience of women with early primary breast cancer in the adjuvant setting suggests that the benefit of endocrine therapy alone in patients with oestrogen receptor (ER)-positive tumours is greater than that achieved with chemotherapy alone (Scottish Cancer Trials Breast Group and ICRF Breast Unit, Guy’s Hospital, London 1993, Ejlertsen et al. 1999, Jakesz et al. 1999). Furthermore, the use of preoperative endocrine therapy has fewer side effects than chemotherapy and also has the potential advantage that it can be continued throughout the perioperative period. Preoperative endocrine therapy in breast cancer should be evaluated in well-designed trials to delineate its precise role.

The present review covers the rationales of preoperative systemic therapy, draws conclusions from currently available studies, and sheds light on directions for future research in this area.

Rationales of preoperative systemic therapy

At least two parameters (local control and survival) need to be examined when any form of systemic therapy for breast cancer is being evaluated. Preoperative systemic therapy has
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the potential capability of downstaging breast cancer, thereby making inoperable tumours operable, and reducing large operable tumours to a size at which breast conservation rather than mastectomy could be performed. With the use of preoperative systemic therapy, local control of disease may therefore be achieved by less aggressive surgery. Furthermore, it is possible that initial tumour regression before surgery might actually result in better local control compared with that achieved by surgery alone. However, although downstaging of tumours – even to the extent of carrying out breast conservation for large tumours on presentation – is feasible and seems to be a potential benefit of preoperative systemic therapy, the long-term outcome results (e.g. rate of recurrence in the ipsilateral breast) must be considered. The National Surgical Adjuvant Breast and Bowel Project B18 study (Fisher et al. 1997) showed that, in some patients with large primary tumours at presentation, the tumour could be downstaged and treated by breast conservation, but that this resulted in a significantly greater local recurrence rate compared with that in patients who had tumours suitable for breast conservation at presentation (14.5% compared with 6.9%) (Fisher et al. 1997, 1998).

The potential for preoperative systemic endocrine therapy to affect survival also needs to be examined carefully. Despite the fact that a significant survival advantage of neoadjuvant compared with adjuvant chemotherapy was not shown in randomised studies, there are at least theoretical reasons why preoperative endocrine therapy might produce a survival advantage over adjuvant endocrine therapy:

1. One possible reason is that preoperative endocrine therapy could be continued during the perioperative period. Scientific work has suggested the possibility of tumour shed and metastatic potential during this period (Fisher & Mamounas 1995).

2. In the adjuvant setting, assessment of therapeutic response is not possible and therapies are therefore given on the basis of an estimated probability of benefit. A further advantage of preoperative systemic therapy is that the primary tumour can be used as a marker of response to a therapeutic regimen. Preoperative use of systemic therapies could allow toxic and ineffective regimens to be discontinued early (thereby reducing the side effects), whereas agents that induced a satisfactory initial response could be continued as adjuvant therapy. The latter would be particularly true of endocrine therapies. This targeting of systemic therapies would reduce the number of patients suffering from side effects unnecessarily, and might also have a favourable impact on survival.

3. Animal studies demonstrated an increase in the labelling index of the metastases, with an increase in the size of the metastases after removal of the primary tumour (Fisher et al. 1989a). Similar kinetic changes in distant tumours were also seen after primary tumour radiotherapy. Studies showed that such stimulation of residual tumour cell growth after removal or irradiation of the primary tumour was due to a serum growth factor; prior treatment with chemotherapy or tamoxifen was able to suppress this effect and prolong survival (Fisher et al. 1989b). Extrapolation of this experimental model to human beings would mean that preoperative systemic therapy could be advantageous and, as suggested above, might potentially result in a survival benefit by inhibition of surgically induced tumour growth.

4. Furthermore, it has been hypothesised that, as a tumour cell population increases, there is an expanding number of drug-resistant phenotypic variants that arise as a result of spontaneous somatic mutations (Goldie & Coldman 1979). This would provide another reason for instituting systemic therapy before operation.

Review of studies

Few studies have been conducted solely to evaluate the precise role of preoperative endocrine therapy for primary breast cancer; however, a number of phase II and a few randomised studies have been conducted on the use of endocrine therapy as the initial therapy for primary breast cancer and their findings provide important data in relation to the use of preoperative endocrine therapy and the design of future trials. Major studies, first on primary use of endocrine therapy (use of endocrine therapy as sole therapy for treatment of primary breast cancer), and then on preoperative endocrine therapy (use of endocrine therapy before surgery for primary breast cancer) will be described, followed by a discussion on the insights gained from these studies.

The conventional assessment criteria laid down by the International Union Against Cancer (UICC) (Hayward et al. 1977) have been used in most studies, and the discussion with regard to response status will be based on them. However, different methods (including measurements of tumour volume, for instance) have also been used in some studies, which has made comparison with other studies difficult.

Primary use of endocrine therapy

Potentially operable primary breast cancer

Phase II studies

Most studies of endocrine therapy used as sole treatment for primary breast cancer were phase II studies started in the late 1970s and the 1980s, when clinicians tried to avoid surgery in elderly or unfit patients with operable primary breast cancer. The rationale for this approach was that elderly patients often had intercurrent illnesses, which might make surgery hazardous, and from which they might die if tamoxifen provided long-term control of their
tumour. The first phase II study was reported in 1982 (Preece et al. 1982), followed by a number of studies of similar nature. Complete and partial responses were achieved in 37–81% of patients after a mean period of approximately 1.5–9 months. In these initial studies, patients were unselected in terms of ER status and tamoxifen was used as the form of endocrine therapy. However, it should be noted that the percentage of patients with an ER-positive tumour increases with increasing age (Clark et al. 1984). The elderly were therefore the ideal patient population in whom to test the concept of primary endocrine therapy – having a high proportion of ER-positive tumours and other intercurrent illnesses that might be a significant mortality risk. The details of these studies are summarised in Table 1. Essentially, the results of all these phase II studies have shown that an objective response (complete response + partial response) would be achieved in a proportion of operable primary breast cancers (between 33% and 67% in unselected patients) by initial use of tamoxifen alone. However, the time taken to achieve a partial response could be as long as 9 months, and it could take even longer to achieve a complete response.

Comparative/randomised studies
Several comparative or randomised studies have evaluated the use of primary endocrine therapy for patients with potentially operable primary breast cancer by comparing it with other modalities of treatment, such as chemotherapy (Table 2). The Royal Marsden group treated 57 patients with operable but large primary breast cancer with either initial endocrine therapy (n = 42) or chemotherapy (n = 15) (Mansi et al. 1989). Initial response (complete response + partial response) rates were greater in the chemotherapy group (60% compared with 47%) and only one and two patients respectively progressed early on initial chemotherapy and endocrine therapy. None had uncontrollable local recurrence and eventually only 18% of patients underwent mastectomy, 30% had radiotherapy and the remainder were still maintained on primary medical therapy after a median follow-up of 19 months. Another subsequent report came

Table 1  Phase II studies on the primary use of endocrine therapy for potentially operable primary breast cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Recruitment</th>
<th>Stage</th>
<th>n</th>
<th>Response</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preece et al. 1982</td>
<td>&gt;75 years</td>
<td>T2–4</td>
<td>67</td>
<td>73%</td>
<td></td>
</tr>
<tr>
<td>Helleberg et al. 1982</td>
<td>&gt;65 years</td>
<td>T1–2</td>
<td>26</td>
<td>CR = 75%</td>
<td></td>
</tr>
<tr>
<td>Bradbeer &amp; Kyngdon 1983</td>
<td>&gt;70 years</td>
<td>T1–3</td>
<td>161</td>
<td>CR = 27%</td>
<td>CR + PR in 78% in 6 months</td>
</tr>
<tr>
<td>Allan et al. 1985</td>
<td>&gt;60 years</td>
<td>T1–3</td>
<td>53</td>
<td>CR = 55%</td>
<td>Median time to CR/PR = 15.5 weeks</td>
</tr>
<tr>
<td>Nicholson et al. 1988</td>
<td>Elderly</td>
<td></td>
<td>61</td>
<td>CR = 18%</td>
<td></td>
</tr>
<tr>
<td>Margolese &amp; Foster 1989</td>
<td>&gt;78 years</td>
<td>T1–3</td>
<td>30</td>
<td>CR = 17%</td>
<td></td>
</tr>
<tr>
<td>Akhtar et al. 1991</td>
<td>&gt;70 years or frail</td>
<td>100</td>
<td></td>
<td>CR = 40%</td>
<td>Median time to CR/PR = 13.5/14 weeks</td>
</tr>
<tr>
<td>Foudraine et al. 1992</td>
<td>&gt;67 years</td>
<td></td>
<td>40</td>
<td>Remission = 42.5%</td>
<td>Mean time to remission = 8.9 months</td>
</tr>
<tr>
<td>Gaskell et al. 1992</td>
<td>&gt;70 years</td>
<td></td>
<td>66</td>
<td>CR = 21%</td>
<td>Significant regression in 29% in 3 months</td>
</tr>
<tr>
<td>Van Dalsem &amp; de Vries 1995</td>
<td>&gt;70 years</td>
<td>T1–4</td>
<td>34</td>
<td>Good local control in 74%</td>
<td></td>
</tr>
<tr>
<td>Bergman et al. 1995</td>
<td>&gt;75 years</td>
<td></td>
<td>85</td>
<td>CR = 14%</td>
<td>Median time to CR/PR = 6–7 months</td>
</tr>
<tr>
<td>Ciatto et al. 1996</td>
<td>&gt;70 years</td>
<td></td>
<td>120</td>
<td>CR = 10%</td>
<td></td>
</tr>
</tbody>
</table>

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

www.endocrinology.org
Table 2 Comparative/randomised studies on the primary use of endocrine therapy for potentially operable primary breast cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Recruitment</th>
<th>Treatment arms</th>
<th>Response</th>
<th>Median follow-up (months)</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mansi et al. 1989</td>
<td>Large</td>
<td>Endocrine therapy (n = 42)</td>
<td>CR = 2%, PR = 45%</td>
<td>19</td>
<td>Outcome: mastectomy (18%), radiotherapy (30%), maintained on medical therapy (52%)</td>
</tr>
<tr>
<td></td>
<td>primary</td>
<td>Chemotherapy (n = 15)</td>
<td>PD = 5%, PR = 53%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smith 1991</td>
<td>Stage I–III</td>
<td>Tamoxifen (n = 54)</td>
<td>CR = 4%, PR = 50%,</td>
<td>34</td>
<td>Chemotherapy: cyclophosphamide, methotrexate and 5-fluorouracil, or mitozantrone, methotrexate and mitomycin C</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>SD = 39%, PD = 7% at 3 months</td>
<td></td>
<td>Outcome: mastectomy (20%), uncontrollable local recurrence (4%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chemotherapy (n = 41)</td>
<td>CR = 15%, PR = 51%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>SD = 32%, PD = 2% at 3 months</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

from the same group, involving 54 patients who were treated with initial endocrine therapy for primary breast cancer (Smith 1991). The patients formed part of a study in which another 41 patients received chemotherapy. The 54 patients had tamoxifen because they were either too old for, or they refused, chemotherapy. Endocrine therapy was given for 3 months, with responses as follows: complete response = 4%, partial response = 50%, stable disease = 39% (including minimal response in 26%) and progressive disease (PD) = 7%. Their chemotherapy counterparts had greater response rates: complete response = 15%, partial response = 51%, stable disease = 32% (including minimal response in 22%) and progressive disease = 2%.

There have been a series of randomised trials that have investigated the use of primary tamoxifen therapy in elderly patients with operable primary breast cancer (Table 3). Two randomised trials initiated in the early 1980s compared tamoxifen as sole therapy and surgery as sole therapy. One study of 135 patients with operable primary breast cancer (stage I/II), unselected for ER status of the tumour, were allocated randomly to groups to receive either tamoxifen 20 mg daily or wedge mastectomy (Robertson et al. 1988). Objective remission plus stable disease was achieved in 74% (59% objective response at 6 months). A recent report of the long-term follow-up data of this trial showed no significant difference in survival or rate of metastases after a median follow-up of 145 months. The group treated with mastectomy had, however, a significantly lower local recurrence rate than those treated initially by tamoxifen only (Kenny et al. 1998).

Similar overall survival and metastasis-free survival were demonstrated by Gazet et al. (1988), who reported a similar randomised trial at the same period. A total of 116 elderly patients with operable primary breast cancer were allocated randomly to groups to receive either tamoxifen or surgery as sole initial treatment. Unlike the findings of the study reported by Robertson et al. (1988), after 3 years, progression in the tamoxifen arm of the study was no worse than local relapse in the surgery arm, and there was no difference in the disease-free survivals. However, the study has been criticized: for example, some patients appeared to have received inadequate surgery, as a number of patients with locally advanced primary tumours were treated by breast conservation. This would have increased the local recurrence rate in the surgically treated group.

Further randomised studies in elderly patients with operable primary breast cancer have compared tamoxifen as sole initial treatment and surgery with adjuvant tamoxifen. An Italian multicentre trial that recruited 473 patients showed no difference in overall survival or metastasis-free survival (Mustacchi et al. 1994). As with the studies reported by Robertson et al. (1988) and Kenny et al. (1998), the local control in the tamoxifen-only group was less good than that in the surgery (plus tamoxifen) group in the Italian studies (225% compared with 6% local recurrence/progression rates at 3 years). Similar results were also seen in the Cancer Research Campaign trial, which studied 381 patients (Bates et al. 1991). The local relapse rate was again much greater in the tamoxifen-only group than in the surgery plus adjuvant tamoxifen group (28% compared with 12%). Therefore endocrine therapy, though not being able to induce as rapid a response as chemotherapy, does produce responses in a significant number of elderly patients with operable primary breast cancer unselected for ER status. However, the local relapse rate is greater than the recurrence rate after surgery with or without tamoxifen.

In a later trial in which only patients with ER-positive tumours having an H score of at least 100 (maximum H score = 300 by immunohistochemical assay) were included (a total of 147 patients randomised), the Nottingham group reported that the rates of clinical benefit (objective response + stable disease) and of objective response increased to 97% and 74%.
Table 3 Comparative/randomised studies on the primary use of endocrine therapy for potentially operable primary breast cancer in the elderly

<table>
<thead>
<tr>
<th>Study</th>
<th>Recruitment</th>
<th>Treatment arms</th>
<th>Response</th>
<th>Median follow-up</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gazet et al. 1988</td>
<td>&gt;70 years</td>
<td>Tamoxifen (n = 60)</td>
<td>Local failure = 25%</td>
<td>3 years</td>
<td>No difference in survival</td>
</tr>
<tr>
<td></td>
<td>Operable primary</td>
<td>Surgery (n = 56)</td>
<td>Local recurrence = 38%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bates et al. 1991</td>
<td>&gt;70 years</td>
<td>Tamoxifen (n = 183)</td>
<td>Local failure = 28%</td>
<td>34 months</td>
<td>No difference in survival</td>
</tr>
<tr>
<td></td>
<td>Operable primary</td>
<td>Surgery + adjuvant tamoxifen (n = 171)</td>
<td>Local recurrence = 12%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mustacchi et al. 1994</td>
<td>&gt;70 years Operable primary</td>
<td>Tamoxifen (n = 236)</td>
<td>Local failure = 25%</td>
<td>3 years</td>
<td>No difference in survival</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Surgery (n = 237)</td>
<td>Local recurrence = 6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Willsher et al. 1997a</td>
<td>&gt;70 years Stage I/II ER +</td>
<td>Tamoxifen (n = 94)</td>
<td>CR = 30%, PR = 44%, SD = 23%, PD = 3% at 6 months; eventual local failure = 32%</td>
<td>3 years</td>
<td>*16% required mastectomy</td>
</tr>
<tr>
<td>Kenny et al. 1998</td>
<td>&gt;70 years Stage I/II Unselected for ER</td>
<td>Tamoxifen (n = 66)</td>
<td>CR = 42%, PR = 17%, SD = 15%, PD = 26% at 6 months; eventual local failure = 81%</td>
<td>12 years</td>
<td>No difference in survival</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Wedge mastectomy (n = 65)</td>
<td>Local recurrence = 38%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

respectively (Willsher et al. 1997a). In this later study, the number of ER-positive tumours that progressed early during initial endocrine therapy was very small. The concern that a significant number of patients might progress in the first 3 months of endocrine therapy because of the slower rate of action of this technique seems unfounded in such a population of patients with strongly ER-positive tumours.

None of the individual randomised trials have shown significant difference in survival between patients treated with initial endocrine therapy and those given surgery with or without adjuvant endocrine therapy. However, it should be noted that the power of all these individual trials is low, and the results from these randomised trials do not confirm equivalence of tamoxifen as sole initial therapy with surgery, with or without adjuvant endocrine therapy. In fact a combined analysis of two randomised trials comparing tamoxifen and surgery and adjuvant tamoxifen showed a non-significant divergence of the overall survival curves, with a significant difference in breast-cancer-specific mortality in favour of the surgically treated group after approximately 4 years of follow-up (Mustacchi et al. 1998). Longer follow-up will be required for careful evaluation of any differences between these different treatment regimes.

The randomised trials are in agreement that surgery, either as sole initial therapy or followed by adjuvant endocrine therapy, provides better local control than initial endocrine therapy alone.

**Locally advanced primary breast cancer**

Most studies on the use of endocrine therapy for locally advanced primary tumours involved comparison of initial primary endocrine therapy with other modalities of initial treatment, for example surgery, radiotherapy and chemotherapy.

The Nottingham group reported two randomised trials of the use of endocrine therapy as sole initial treatment in patients with locally advanced primary breast cancer. The first trial, reported initially in 1988, compared tamoxifen with radical radiotherapy (Williams et al. 1988). Long-term results were published at a median follow-up of nearly one decade (Willsher et al. 1996). In this trial, 73 patients were allocated randomly to groups to receive initial tamoxifen, while 70 received initial radiotherapy and treatment was crossed over when the first modality of therapy failed. Objective response plus stable disease were achieved at 6 months in 78% of patients receiving tamoxifen (43%
objective response). Subgroup analysis showed that 85% of patients with ER-positive tumours achieved objective response + stable disease, compared with only 57% in patients with ER-negative tumours. Although there was no difference in the overall survival between patients treated initially with tamoxifen or radiotherapy, a non-significant divergence in favour of the initial tamoxifen group was seen in the metastasis-free survival.

The second randomised trial in locally advanced primary breast cancer compared endocrine therapy as sole initial treatment with multi-modality therapy (neoadjuvant chemotherapy, modified radical mastectomy, postoperative radiotherapy and adjuvant endocrine therapy) (Willsher et al. 1997b). Objective response and stable disease were achieved at 6 months of initial hormone therapy in 36% and 32% respectively, whereas 57% and 39% of patients had objective response and stable disease respectively after completing neoadjuvant chemotherapy. There was no significant difference in overall survival, metastasis-free interval or in uncontrollable local recurrence at a median follow-up of 30 months. In neither of these two studies was tamoxifen used as neoadjuvant therapy to downstage the primary tumour, therefore no data are available on the use of endocrine therapy in locally advanced disease to increase operability or to make such tumours treatable by breast conservation.

Preoperative endocrine therapy

To date, there have been very few studies on the use of preoperative endocrine therapy aiming, for example, at downstaging of the primary tumour before surgery (Table 4). An early study by the Edinburgh group reported a response in 11 of 23 and 12 of 13 patients receiving preoperative endocrine and cytotoxic therapy respectively for primary breast cancer >4 cm (Forrest et al. 1986). Stimulated by these phase II studies and by the investigators’ own experience of using tamoxifen as primary treatment for elderly patients with primary breast cancer (Gazet et al. 1988), the first randomised trial of preoperative endocrine therapy versus chemotherapy was reported by the Royal Marsden Hospital in 1991 (Gazet et al. 1991). Thirty patients with locally advanced primary breast cancer were recruited in each arm. Responders would be subjected to wide local excision or mastectomy. Those who achieved complete response had either surgery or radiotherapy, according to their (the patient’s) choice. Those whose tumour failed to reduce in size received radiotherapy. After 12 weeks of treatment, 27% of patients receiving chemotherapy had a complete response, another 27% had >50% reduction of tumour size, and 33% of them had 25–50% reduction; only 13% failed to respond. In contrast, only 10% of patients receiving endocrine therapy had a >50% reduction and 13% had a 25–50% reduction in tumour size. The tumour appeared unchanged in 40% and progressed in 37%. Although chemotherapy was significantly more effective than endocrine therapy in inducing a response at the end of a 12–week treatment, there was no significant difference in the disease-free survival or the rate of metastases in this study.

The same group also published a further study (Gazet et al. 1996). In this study, the choice of preoperative systemic therapy was based on ER status of the tumour. Patients with ER-negative tumours received chemotherapy, and those with ER-positive tumours were treated with endocrine therapy for a period of 3 months, as in the first trial. With such a patient selection, the objective response rates were 60% for chemotherapy and 40% for endocrine therapy.

After their initial publication in 1986, the Edinburgh group have reported on the use of preoperative endocrine therapy (including oophorectomy, goserelin and aminoglutethimide) in 61 patients (aged 33–69 years) with large operable primary breast cancer >4 cm (Anderson et al. 1989, 1991). At 3 months, significant regression (reduction to at least half of the initial tumour volume) was achieved in 39%. The mean time to such regression was 44 days (range: 3–150 days). More recently, the same group have reported very high response rates with the use of the new selective third-generation aromatase inhibitors (Dixon et al. 1999a, b). Twenty-four patients (61–87 years) with ER-positive tumours >3 cm were treated with letrozole, resulting in the following clinical responses: seven complete responses (29%), 16 partial responses (67%) and one stable disease (4%). The radiological responses were: one complete response (4%), 21 partial responses (88%) and two stable diseases (8%). Fifteen of the 24 patients were able to undergo breast conservation after treatment (Dixon et al. 1999a). A similar study reported no complete responses, 18 partial responses (78%) and five stable diseases (22%) (radiological responses) at 3 months when anastrozole was used in 23 patients. Fifteen of the 23 patients with tumours originally requiring mastectomy became suitable for breast conservation (Dixon et al. 1999b).

A recent review of the long-term survival data in a non-randomised study (by the Edinburgh group) of 94 patients who had preoperative systemic therapy for large tumours >4 cm showed no difference in survival between those treated with endocrine and cytotoxic therapies (Cameron et al. 1997). Data also suggest that patients with an ER-positive tumour tend to have good prognosis after preoperative endocrine therapy alone (i.e. not necessarily combined with neoadjuvant chemotherapy).

Conclusions

Primary use of endocrine therapy is not recommended, because of its poor long-term local control and should only be considered for the very frail patient with a limited life expectancy. Nevertheless, the evidence with regards to inducing a response seen in the primary use of endocrine
therapy has substantiated the use of endocrine therapy in a preoperative setting.

On average, endocrine therapy produces an objective response in about 50% of the patients with primary breast cancer unselected by ER status, although it should be remembered that the studies have mainly been conducted in elderly patients, the majority of whom should have ER-positive tumours. However, the objective response rate can be increased to 70% if only patients with a known ER-positive tumour are included. The latter figure is comparable to the results obtainable using neoadjuvant chemotherapy. It has been a general belief that endocrine therapy takes time to achieve an objective response, usually between 3 and 6 months, whereas chemotherapy often results in an earlier response (2–3 months). In most early studies, tamoxifen was the endocrine agent most frequently used and it appears that new endocrine agents e.g. third-generation non-steroidal aromatase inhibitors such as anastrozole and letrozole may produce a better quality of response (i.e. complete response rather than partial response) and more

**Table 4 Studies on the preoperative use of endocrine therapy**

<table>
<thead>
<tr>
<th>Study</th>
<th>Recruitment</th>
<th>Treatment arms</th>
<th>Response</th>
<th>Median follow-up</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forrest et al. 1986</td>
<td>&gt;4 cm operable primary</td>
<td>Endocrine therapy (n = 23) Combination chemotherapy (n = 13)</td>
<td>Response = 48%</td>
<td>3 years</td>
<td>*Histological CR in 42%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chemotherapy (n = 47)</td>
<td>Response = 92%*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anderson et al. 1989, 1991</td>
<td>&gt;4 cm operable primary</td>
<td>Endocrine therapy (n = 61)</td>
<td>Significant regression = 0%, SD = 33% at 12 weeks if ER &lt;20 fmol</td>
<td></td>
<td>Endocrine therapy: oophorectomy (n = 5) goserelin (n = 19), tamoxifen (n = 11), aminoglutethimide (n = 10), 4-hydroxyandrostenedione (n = 16) Chemotherapy: cyclophosphamide, doxorubicin, vincristine, prednisolone Significant regression = &gt;50% reduction in tumour volume</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chemotherapy (n = 47)</td>
<td>Significant regression = 52% SD = 35% at 12 weeks if ER &gt;20 fmol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gazet et al. 1991</td>
<td>Stage III (n = 30)</td>
<td>Endocrine therapy (n = 30)</td>
<td>CR = 0%, PR = 10%, SD = 53%, PD = 37% at 12 weeks</td>
<td>65 weeks</td>
<td>27 patients had breast conservation No difference in local recurrence, metastases and survival</td>
</tr>
<tr>
<td>Gazet et al. 1996</td>
<td>Stage I–III (n = 47)</td>
<td>Endocrine therapy (n = 47)</td>
<td>Response at 3 months = 40% (CR in stage I/II:III = 20%:0%)</td>
<td></td>
<td>Endocrine therapy: goserelin (leuprolide) (premenopausal) and 4-hydroxyandrostenedione (formestane) (postmenopausal) Chemotherapy: mitozantrone, methotrexate and mitomycin C 84% of CR had residual tumour on histology</td>
</tr>
<tr>
<td>Dixon et al. 1999a</td>
<td>61–87 years</td>
<td>Letrozole (n = 24)</td>
<td>CR = 29%, PR = 67%, SD = 4%</td>
<td></td>
<td>15 patients had breast conservation</td>
</tr>
<tr>
<td></td>
<td>&gt;3 cm ER+ (n = 53)</td>
<td>Chemotherapy + if ER−</td>
<td>Response at 3 months = 60% (CR in stage I/II:III = 41%:14%)</td>
<td></td>
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</table>

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.
rapid response rates compared with tamoxifen. However, these observations need to be confirmed in large prospective randomised trials. A reassuring feature from the more recent studies is that a patient with an ER-positive tumour is unlikely to have progressive disease within the 3 months of preoperative therapy. These data would support the use of preoperative endocrine therapy in the context of studies of ER-positive tumours and allow the clinicians to reassure patients that the cancer should not progress on such treatment.

**Future directions**

Where are we now and what should be looked at in current and future studies? With the encouraging results from phase II and randomised studies and the known advantages of endocrine therapy over chemotherapy in terms of side effects and the possibility of continued therapy perioperatively, the role of preoperative endocrine therapy should be pursued and better defined. There are a number of questions that need to be dealt with by further studies, both in the laboratory and in clinical trials.

The first question to answer is, ‘What should be the indication for preoperative endocrine therapy?’ As mentioned at the very beginning, the two parameters for evaluating a systemic therapy for breast cancer are local control and survival. Could preoperative endocrine therapy be used effectively to downstage the tumour hence increasing operability and making breast conservation a safe option? The use of neoadjuvant chemotherapy in locally advanced primary breast cancer has been very popular and the use of endocrine agents instead in a selected subgroup of patients with ER-positive tumours should be investigated. Clinical trials to investigate these potential advantages in early primary breast cancer should be carried out. However, perhaps more importantly, a comparison between pre- and perioperative endocrine therapy and the conventional adjuvant therapy (postoperative) is mandatory and particular attention should be drawn to defining a survival benefit.

It would appear from the review of various studies that future preoperative endocrine therapy trials should concentrate on patients with ER-positive tumours. The response rates for ER-negative tumours have been shown to be much lower for endocrine therapy than for chemotherapy. However, a relatively large proportion of patients progressed during the course of medical treatment (whether chemotherapy or endocrine therapy), and this could be detrimental when any preoperative systemic therapy is used. This was not only true when tamoxifen was used to treat ER-negative tumours, but should also apply to other endocrine agents, including the new aromatase inhibitors (Evans 1994) and, to a lesser extent, to chemotherapy.

Maximal response seems to occur at around 3 months or even later with the use of preoperative endocrine therapy. The optimum duration of treatment to achieve the best possible and useful (in terms of downstaging) response has to be defined by trials, so that patients could be subjected to surgery at the appropriate time without jeopardising the locoregional control. These trials could complement laboratory research on new techniques to monitor response, in order to select out non-responders, again at the appropriate time.

Another important issue is the selection of which endocrine agent to use. As mentioned above, tamoxifen was used in most early studies, and the use of new agents such as the third-generation non-steroidal aromatase inhibitors (e.g. letrozole and anastrozole) seems to produce a better response rate in small non-randomised series of patients (Dixon et al. 1999a,b). Further studies on preoperative endocrine therapy should therefore include new agents, in addition to tamoxifen, which has been the standard first-line endocrine therapy in postmenopausal patients. The new antioestrogens (e.g. long-acting ICI 182,780 (Faslodex, AstraZeneca)) and aromatase inhibitors (e.g. anastrozole and letrozole) appear to have potential advantages over tamoxifen, as they have rapid and profound inhibitory activities, few or no agonist effects, and low side-effect profiles (Howell et al. 1998). A recent report of a pre-surgical study comparing Faslodex (in different doses) with tamoxifen and with placebo confirmed that the pure antioestrogen, Faslodex, produced a more rapid and significantly greater decrease in oestrogen and progesterone receptors than did tamoxifen (Robertson et al. 1999). These biological data further emphasise the potential clinical benefits that may be expected with a pure antioestrogen. Another area that is worthy of further attention is the potential benefit of combination endocrine therapy and combined endocrine and chemotherapeutic, especially in the context of locally advanced primary breast cancer (Oliver 1996).

All the above issues can be resolved only by carrying out randomised trials; there are other issues that can be dealt with by clinical and laboratory studies.

One concern as to the use of preoperative systemic therapy is that the traditional prognostic information e.g. nodal status might be altered or lost. A potential solution is the use of immunohistochemical and immunocytochemical techniques to define other tumour markers of prognostic significance – for example, epidermal growth factor receptor (EGFR), Ki67 labelling index indicative of nuclear proliferation, pS2, c-erbB2 and cathepsin D. As seen from the results of various studies, ER is a very important factor in the selection between endocrine and cytotoxic therapies to be used preoperatively. Measurement of the above factors, rather than ER alone, could delineate a more suitable group of patients who would benefit most from preoperative endocrine therapy. There are reports suggesting an association of ER negativity, high Ki67 labelling index and EGFR overexpression with shortened time to progression and
survival in patients treated with endocrine therapy (Sainsbury et al. 1987, Archer et al. 1995). The presence of the pS2 protein has been shown to predict a better response in patients receiving tamoxifen for primary breast cancer (Soubeyran et al. 1996). These techniques can also allow monitoring of response through sequential biopsy sampling during the course of preoperative treatment (Bajetta et al. 1998). Optimum selection of patients for better targeted therapy may become feasible. The use of preoperative endocrine therapy can also provide an in vivo model in which to evaluate all those biological markers that will be useful in prognostication, prediction and monitoring of response.

As it takes longer for endocrine therapy to act, it seems vital to identify non-responders early in the course of treatment, so that they can be offered alternative therapies. Defining the best way to monitor response is therefore of paramount importance. Apart from improving the prediction of response using laboratory techniques to identify tissue markers as mentioned, methods of objective measurements of the tumour should also be agreed. The conventional way to monitor therapeutic response to systemic therapy in advanced breast cancer is by criteria laid down by the UICC (Hayward et al. 1977), which were used in most studies. Clinical bi-dimensional measurements by callipers are generally used. The Edinburgh group attempted to improve its accuracy by measuring the diameters in eight dimensions and then calculating the tumour volume. Linear regression analysis of the sequential tumour volumes was carried out (Anderson et al. 1989, 1991); inter-observer variability could be great in clinical measurement. Mammography has not yet been shown to be useful, often because tumours tend to have ill-defined margins and significant discrepancy from clinical measurements exists (Smith 1991, Moskovic et al. 1993). Ultrasonography could be an alternative, but probably its use is not worthwhile in the case of large tumours. Changes in vascularity as measured by colour Doppler flow imaging have also been reported as a potential parameter for measuring response to medical therapy in breast cancer (Kedar et al. 1994).

Summary

Preoperative systemic therapy for breast cancer could downstage a primary tumour hence increasing operability and making breast conservation feasible. Whether it could achieve a clinically significant survival benefit remains to be elucidated. Preoperative endocrine therapy, in contrast to neoadjuvant chemotherapy, carries fewer side effects and can be continued throughout the perioperative period. In patients with an ER-positive tumour, a response approaching 70% could be reached in approximately 3 months using traditional endocrine manipulation such as tamoxifen; the tumour seldom progresses during this period. Further studies are required to identify factors (in addition to ER) that would predict the response precisely, to select appropriate patients, to define the optimum duration of therapy, to improve existing methods of monitoring response, to identify the best endocrine agents, and to demonstrate the superiority of pre- and perioperative endocrine therapy over conventional adjuvant endocrine therapy in patients with early breast cancer.

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