Monotherapy of Metastatic Breast Cancer: 
A Review of Newer Agents

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ABSTRACT

Purpose. New agents for the palliative treatment of metastatic breast cancer have emerged in the 1990s. This review summarizes the response rates of these agents with an emphasis on recent findings, such as presentations from the 1998 Meeting of the American Society of Clinical Oncology.

Methods. The English medical literature was reviewed to identify clinical trials involving monotherapy for the treatment of metastatic breast cancer. Three agents—paclitaxel, vinorelbine, and docetaxel—are emphasized because their databases are extensive enough to allow interesting comparisons. Liposomal-encapsulated anthracyclines, losoxantrone, gemcitabine, oral surrogates of continuous-infusion fluorouracil, raltitrexed, LY 231514, edatrexate, topoisomerase I inhibitors, and trastuzumab are reviewed briefly.

Results. Many of the new agents produce response rates approaching or even surpassing those achievable with doxorubicin monotherapy. Compared with older agents, some new agents have improved or at least different safety profiles, and some are easier to administer.

Discussion and conclusions. The new agents offer useful therapeutic options that make them suitable for combining with each other and with older agents, which could result in more effective regimens for metastatic disease, and, ultimately, primary disease in the adjuvant setting. The chemotherapeutic paradigms governing the management of breast cancer for the past three decades are likely to change as we move into the 21st century.

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INTRODUCTION

The modern era of cytotoxic chemotherapy for metastatic breast cancer was initiated by the seminal studies of Greenspan et al [1] and then Cooper [2]. In the late 1970s, combinations of cyclophosphamide, methotrexate, and fluorouracil (CMF), with or without vincristine and with or without prednisone, dominated therapeutic practice for metastatic disease and later as adjuvant therapy [3, 4]. The introduction of doxorubicin [5] and, later, mitoxantrone [6] and epirubicin [7], provided additional options and possible advantages. Generally, however, no further advances in the chemotherapeutic management of metastatic breast cancer occurred for more than two decades. Chemohormonal strategies were investigated but yielded no significant improvement over the sequential use of chemotherapy and hormonal therapy [8]. Early attempts to increase dose intensity improved response rates but not survival [9, 10]. In the late 1980s, many studies compared anthracycline- and CMF-based regimens, but only modest improvements were noted for the anthracyclines [11].

In the 1990s, the paradigm of using established combination chemotherapy [1, 2, 9, 11] is shifting to the dose-dense strategy of sequentially administering single agents, as espoused by Gilewski and Norton [12], and others. The shift is even more dramatic in the United States where dose-intensive chemotherapeutic strategies are used with peripheral blood stem cell support [13, 14], despite the lack of convincing evidence of prolonged overall survival to date [14-17]. The positive results of the phase III trial reported by Bezwoda et al. [18] have caused considerable controversy. The results of additional phase III trials are anxiously awaited.

The 1990s have also been an exciting time for breast cancer new drug development. New agents offer attractive therapeutic options because some induce response rates at least equivalent to those of older agents, have improved safety profiles, or are easier to administer. This article reviews data
on the use of new agents as monotherapy for metastatic breast cancer. Three new agents—paclitaxel, vinorelbine, and docetaxel—are emphasized because their databases are extensive enough to allow interesting comparisons.

**Paclitaxel**

Paclitaxel (Taxol®) has been investigated for more than 25 years, but it was not until the late 1980s that management and prevention of hypersensitivity reactions allowed more thorough appraisal of this important drug’s therapeutic activity [19]. This prototypical taxane is a spindle-active compound that stabilizes the microtubular array of the mitotic spindle. The drug captured the attention of the oncology community and desperate patients in the early 1990s because of significant antitumor activity in ovarian cancer [20]. Paclitaxel also captured the attention of the lay press because its sparse initial supply from the bark of the Pacific yew tree triggered debates regarding the need to balance environmental concerns with human welfare.

**First-Line Monotherapy**

In the two initial publications involving breast cancer, Reichman et al. [21] and Holmes et al. [22] reported that single-agent paclitaxel provided response rates of approximately 60% in two small series of chemotherapy-naive patients (Table 1). This response rate was particularly impressive compared with the 43% response rate seen with single-agent doxorubicin in a historical control series [23]. Results of subsequent phase II trials showed lower and more variable response rates, ranging from 15% to 50% (Table 1), which may be due to differences in the dose and schedule of paclitaxel. There was some evidence of a dose-response relationship in noncomparative trials as the response rates associated with 250 mg/m² (32% to 62%) [21, 22, 24-26] tended to exceed those associated with 175 or 135 mg/m² (15% to 36%) [27-30]. Nabholtz et al. [29] observed a trend toward a higher response rate with the higher dose in a randomized comparison of 175 versus 135 mg/m², but the difference was not significant in the subset that received paclitaxel as first-line therapy (36% versus 29%) or even all patients, including those who received paclitaxel as second-line therapy (29% versus 22%; p = .1).

The most commonly used 3-h schedule yielded response rates ranging from 15% to 44% [24-26, 28, 31-33]. A 24-h infusion of 250 mg/m² produced a better response rate (50% versus 40%; p = .02) than the 3-h infusion in the NSABP B-26 Trial [24]. In contrast, the response rates for the 24-h versus 3-h infusions were similar (32% versus 29%; p = .7) when the dose was only 175 mg/m² in patients with previously treated metastatic disease [26]. Collectively, these results demonstrate that the dose and schedule play a combined role, and that the optimal way to use paclitaxel remains uncertain and requires further evaluation.

Paclitaxel was compared with other agents in three large-scale, randomized trials which were presented in 1997. Single-agent paclitaxel appeared to produce results equivalent to those of doxorubicin 60 mg/m² [27], but inferior to those of doxorubicin 75 mg/m² [33], and equivalent to those of CMF plus prednisone [32]. It should be noted, however, that different doses and schedules of paclitaxel were administered in these three trials (Table 1).

**Second-Line Monotherapy**

Market research surveys indicate that paclitaxel is the most commonly used agent in the United States after failure of first-line treatment. Seidman et al. [35] reported an impressive response rate of 44% with high-dose paclitaxel infused over 24 h, but response rates have been lower with other doses and schedules (Table 2) [26, 29, 33, 34,36-44]. In fact, the majority of response rates appear to cluster at ≤25%. There may be a steep dose-response curve, with differences between the 200- and 250-mg/m² doses using 3-h or 24-h infusions. However, Winer et al. [37] could not detect any significant differences in response rates or survival in a randomized comparison of paclitaxel 250, 210, or 175 mg/m² over 3 h.

Alternate schedules are being evaluated. Promising results with 96-h paclitaxel infusions in patients resistant to anthracyclines [45] or 3-h infusions of paclitaxel [46] led to a large randomized phase III trial at the M.D. Anderson Cancer Center [38]. There were no significant differences

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**Table 1. Paclitaxel activity as a first-line, single agent in metastatic breast cancer**

<table>
<thead>
<tr>
<th>Dosage schedule (mg/m² per hour)</th>
<th>n of patients</th>
<th>Response rate, %</th>
<th>Authors [reference]</th>
</tr>
</thead>
<tbody>
<tr>
<td>250 (24) + G-CSF*</td>
<td>26</td>
<td>62</td>
<td>Reichman et al., 1993 [21]</td>
</tr>
<tr>
<td>250 (24)</td>
<td>25</td>
<td>56</td>
<td>Holmes et al., 1991 [22]</td>
</tr>
<tr>
<td>250 (24) + G-CSF versus 250 (3)</td>
<td>284</td>
<td>50</td>
<td>Mamounas et al., 1998 [24]</td>
</tr>
<tr>
<td>250 (3) + G-CSF</td>
<td>82</td>
<td>43</td>
<td>Mamounas et al., 1995 [25]</td>
</tr>
<tr>
<td>250 (3)</td>
<td>25</td>
<td>32</td>
<td>Seidman et al., 1995 [26]</td>
</tr>
<tr>
<td>225 (3)</td>
<td>101</td>
<td>44</td>
<td>Bonneterre et al., 1996 [31]</td>
</tr>
<tr>
<td>200 (3)</td>
<td>104</td>
<td>30</td>
<td>Bishop et al., 1997 [32]</td>
</tr>
<tr>
<td>200 (3)</td>
<td>166</td>
<td>25</td>
<td>Gamucci et al., 1998 [33]</td>
</tr>
<tr>
<td>175 (24)</td>
<td>&gt;200</td>
<td>33</td>
<td>Sledge et al., 1997 [27]</td>
</tr>
<tr>
<td>175 (3)</td>
<td>~74</td>
<td>15</td>
<td>Kaufman et al., 1998 [28]</td>
</tr>
<tr>
<td>175 (3) versus 135 (3)</td>
<td>69</td>
<td>36</td>
<td>Nabholtz et al., 1996 [29]</td>
</tr>
<tr>
<td>135 (24)</td>
<td>19</td>
<td>32</td>
<td>Swain et al., 1995 [30]</td>
</tr>
</tbody>
</table>

*G-CSF = granulocyte colony-stimulating factor.
between the 3-h infusion of paclitaxel 250 mg/m² versus the 96-h infusion of 140 mg/m² as measured by response rates (23% versus 29%) or median response durations (4.5 versus 7.5 months). Consequently, Holmes et al. [38] concluded that, while there were trends favoring the 96-h infusion, their data do not justify the extra logistical support required for the prolonged infusion. The results with 1-h weekly paclitaxel infusions initially reported by Hainsworth and Greco [47], and Seidman et al. [48] have stimulated considerable investigative attention. This schedule appears to offer good response rates with better tolerability than do other schedules [49-52].

Antitumor activity in patients previously exposed to anthracyclines was impressive in two series [35, 40], but response rates were usually more modest, ranging from 16% to 26% in other series [26, 29, 33, 36, 42-44]. Of particular note is the crossover response in the EORTC randomized trial [33] comparing paclitaxel 200 mg/m² by 3-h infusion and doxorubicin 75 mg/m². The response rate was lower upon crossover to paclitaxel than to doxorubicin (13% versus 29%); similar trends were seen regardless of whether patients had primary or secondary resistance. This finding, along with the better response to first-line doxorubicin therapy, led Gamucci et al. [33] to conclude that the preferred sequence for monotherapy is doxorubicin followed by paclitaxel.

Safety
Paclitaxel is generally well tolerated at commonly used dosages, especially 175 mg/m² over 3 h, and with weekly 1-h infusions [47-52]. Nausea and vomiting are generally not clinically significant problems. The hypersensitivity reactions, which hindered the early development of paclitaxel, have been almost totally abrogated by premedication with corticosteroids, diphenhydramine, and ranitidine. Granulocytopenia is dose-dependent; granulocyte colony-stimulating factor (G-CSF) is usually given prophylactically with paclitaxel 250 mg/m². Thrombocytopenia is rare. Alopecia is essentially universal with the 3-h and 24-h infusions, but less so with the weekly administration schedule.

The most troubling subjective problem is myalgia and arthralgia syndrome, which can be moderately severe at a dose of 250 mg/m², but much less so at 175 mg/m². The pain associated with this syndrome can be a significant problem, especially at higher doses, but pain is self-limited. Neurosensory changes are common at all doses and more frequent with shorter schedules [24], but neuromotor changes are rare to

### Table 2. Paclitaxel activity as a second-line, single agent in metastatic breast cancer

<table>
<thead>
<tr>
<th>Dosage schedule mg/m² (per hour)</th>
<th>Total n of patients (anthracycline-exposed patients)</th>
<th>Response rate, % (anthracycline-exposed patients)</th>
<th>Authors [reference]</th>
</tr>
</thead>
<tbody>
<tr>
<td>250 (24) versus 200 (24)</td>
<td>25 (25) versus 51 (51)*</td>
<td>44 (44) versus 27 (27)</td>
<td>Seidman et al., 1995 [35]</td>
</tr>
<tr>
<td>250-300 (3)</td>
<td>36 (36)</td>
<td>6 (6)</td>
<td>Vermorken et al., 1985 [36]</td>
</tr>
<tr>
<td>250 (3) versus 210 (3)</td>
<td>-108 (NS)**</td>
<td>22 (NS)</td>
<td>Winer et al., 1998 [37]</td>
</tr>
<tr>
<td>250 (3) versus 175 (3)</td>
<td>-108 (NS)</td>
<td>28 (NS)</td>
<td></td>
</tr>
<tr>
<td>250 (3)</td>
<td>88 (&gt;42)</td>
<td>23 (NS)</td>
<td>Holmes et al., 1998 [38]</td>
</tr>
<tr>
<td>140 (96)</td>
<td>91 (&gt;45)</td>
<td>29 (NS)</td>
<td></td>
</tr>
<tr>
<td>210 (3)</td>
<td>74 (~49)</td>
<td>18 (NS)</td>
<td>Geyer et al., 1996 [39]</td>
</tr>
<tr>
<td>200 (3)</td>
<td>74 (74)</td>
<td>14 (14)</td>
<td>Gianni et al., 1994 [40]</td>
</tr>
<tr>
<td>175 or 225 (3)</td>
<td>50 (50)</td>
<td>38 (38)</td>
<td>Abrams et al., 1995 [41]</td>
</tr>
<tr>
<td>175 (24)</td>
<td>172 (NS)</td>
<td>23 (NS)</td>
<td>Dieras et al., 1995 [43]</td>
</tr>
<tr>
<td>175 (24 or 3)</td>
<td>21 (21)</td>
<td>10 (10)</td>
<td>Seidman et al., 1995 [26]</td>
</tr>
<tr>
<td>175 (3)</td>
<td>36 (~36)</td>
<td>17 (~17)</td>
<td></td>
</tr>
<tr>
<td>175 (3)</td>
<td>24 (24)*</td>
<td>21 (21)</td>
<td>O’Reilly et al., 1998 [44]</td>
</tr>
<tr>
<td>175 (3)</td>
<td>19 (19)</td>
<td>21 (21)</td>
<td></td>
</tr>
<tr>
<td>175 (3) versus 135 (3)</td>
<td>154 (38)</td>
<td>26 (26)</td>
<td>Nabholtz et al., 1996 [29]</td>
</tr>
<tr>
<td></td>
<td>159 (30)</td>
<td>20 (13)</td>
<td></td>
</tr>
</tbody>
</table>

*Third-line chemotherapy.
**Approximately 24% of patients received no prior chemotherapy for metastatic disease.
NS = not stated.
nonexistent at lower doses and usually only mild to moderately severe even at higher doses [26, 29, 35]. Interestingly, Nabholtz et al. [29] reported that 13% to 16% of patients had some degree of edema with paclitaxel. This toxicity is more commonly associated with docetaxel, which will be discussed later in this article.

VINORELBINE

Vinorelbine (Navelbine®) has still not been approved by the Food and Drug Administration (FDA) for breast cancer treatment, despite its good response rates, excellent safety profile, and commercial availability in Europe for this indication. Like paclitaxel, vinorelbine exerts its molecular actions on the mitotic spindle, but like other vinca alkaloids, promotes microtubular depolymerization instead of the stabilization observed with paclitaxel. In contrast with other vinca alkaloids, vinorelbine has greater action on mitotic rather than axonal microtubules, leading to a reduction in the neurotoxicity typically observed with this class of agents [53].

First-Line Monotherapy

As a single agent, first-line vinorelbine produced responses in 35% to 53% of patients with metastatic breast cancer (Table 3) [54-61]. A comparative trial is needed to determine the relative activity of vinorelbine and paclitaxel, which is the focus of large ongoing phase III trials. In the meantime, the relative consistency of results with vinorelbine at a starting dosage of 30 mg/m²/week across a broad array of phase II trials indicates that it may ultimately be shown to be equipotent to the most commonly used doses in the 3-h schedule of paclitaxel.

Second-Line Chemotherapy

The response rate to second-line therapy with vinorelbine ranged from 15% to 47% (Table 4) [61-69], depending on the extent of previous therapy. In patients who had failed CMF, vinorelbine produced a response rate of 32%, similar to that in chemotherapy-naive patients enrolled in the same trial [61]. In contrast, the response rate in two phase II trials, each of which included at least 100 anthracycline-resistant patients, was only 15% or 16% [68, 69]. Although one of these randomized trials showed that vinorelbine was significantly superior to intravenously administered melphalan regarding time to progression, median survival time, and one-year survival [69], the study has been criticized because melphalan is a nonstandard comparator. Another interesting analysis in this trial was prompted by the important observation of Robertson et al. [70] and Howell et al. [71], who concluded that prolonged stable disease (SD) (SD greater than six months), especially in patients with nonmeasurable lesions, provides clinical benefit similar to that experienced by patients with measurable lesions who achieve objective responses (complete response [CR] and partial response [PR]). In the trial by Jones et al. [69], 47% of patients treated with vinorelbine experienced clinical benefit (CR, PR, and SD greater than six months), which is more encouraging than the objective response rate would suggest.

**Table 3. Vinorelbine activity as a first-line, single agent in metastatic breast cancer**

<table>
<thead>
<tr>
<th>n of patients</th>
<th>Response rate, %</th>
<th>Authors [reference]</th>
</tr>
</thead>
<tbody>
<tr>
<td>19</td>
<td>53</td>
<td>Canobbio et al., 1989 [54]</td>
</tr>
<tr>
<td>50</td>
<td>50</td>
<td>Garcia-Conde et al., 1994 [55]</td>
</tr>
<tr>
<td>34</td>
<td>44</td>
<td>Twelves et al., 1994 [56]</td>
</tr>
<tr>
<td>63</td>
<td>44</td>
<td>Bruno et al., 1995 [57]</td>
</tr>
<tr>
<td>145</td>
<td>41</td>
<td>Fumoleau et al., 1993 [58]</td>
</tr>
<tr>
<td>44</td>
<td>41</td>
<td>Romero et al., 1994 [59]</td>
</tr>
<tr>
<td>56*</td>
<td>38</td>
<td>Vogel et al., 1996** [60]</td>
</tr>
<tr>
<td>60</td>
<td>35</td>
<td>Weber et al., 1995 [61]</td>
</tr>
</tbody>
</table>

* All women >60 years of age. ** Data updated from meeting abstract.

**Table 4. Vinorelbine activity as a second-line, single agent in metastatic breast cancer**

<table>
<thead>
<tr>
<th>n of prior regimens</th>
<th>n of patients</th>
<th>Prior doxorubicin therapy, %</th>
<th>Response rate, %</th>
<th>Authors [reference]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>34</td>
<td>&gt;60</td>
<td>47</td>
<td>Ranuzzi et al., 1996 [62]</td>
</tr>
<tr>
<td>1 or 2</td>
<td>30</td>
<td>NS</td>
<td>40</td>
<td>Toussaint et al., 1994 [63]</td>
</tr>
<tr>
<td>1 to 5</td>
<td>67</td>
<td>NS</td>
<td>36</td>
<td>Gasparini et al., 1994 [64]</td>
</tr>
<tr>
<td>≥2</td>
<td>44</td>
<td>100</td>
<td>34</td>
<td>Alvarez et al., 1996 [65]</td>
</tr>
<tr>
<td>1</td>
<td>47</td>
<td>0</td>
<td>32</td>
<td>Weber et al., 1995 [61]</td>
</tr>
<tr>
<td>≥2</td>
<td>33</td>
<td>NS</td>
<td>30</td>
<td>Extra et al., 1991 [66]</td>
</tr>
<tr>
<td>≥2</td>
<td>40</td>
<td>100</td>
<td>25</td>
<td>Livingston et al., 1997 [67]</td>
</tr>
<tr>
<td>≥1</td>
<td>100</td>
<td>100</td>
<td>16</td>
<td>Degardin et al., 1994 [68]</td>
</tr>
<tr>
<td>≥2</td>
<td>115</td>
<td>100</td>
<td>15</td>
<td>Jones et al., 1995 [69]</td>
</tr>
</tbody>
</table>

NS = not stated.
Other study results [62-67] demonstrated higher response rates than those reported by Degardin et al. [68] and Jones et al. [69] when vinorelbine was used after failure of one or more chemotherapy regimens. Livingston et al. [67] reported that a weekly regimen of dose-intensive vinorelbine with G-CSF support produced a 25% response rate in patients failing both anthracycline and paclitaxel therapy. Ranuzzi et al. [62] also used G-CSF and reported a 47% response rate in a small number of patients.

Although determination of the relative activity of vinorelbine and paclitaxel awaits completion of randomized phase III trials, the results from phase II trials of previously treated patients appear to be similar for these two agents at the doses and schedules commonly used. Consequently, therapeutic decisions can be made based on other factors, such as safety profiles.

Safety and Relevant Implications

Vinorelbine is well tolerated. Compared with paclitaxel administered every three weeks, vinorelbine produces equivalent myelotoxicity, but weekly paclitaxel may be less myelotoxic than vinorelbine. Although neither vinorelbine nor paclitaxel produce significant nausea, vinorelbine may have a more favorable safety profile because of its relative lack of alopecia and myalgias. Furthermore, the constipation occasionally encountered with vinorelbine is seldom severe, and neurotoxicity beyond grade 1 is also rare. Finally, vinorelbine does not require premedication with dexamethasone.

Vinorelbine’s two major drawbacks are injection-site reactions and weekly schedule. The reactions can be completely circumvented by using an implanted venous-access device or partially by using a 6-min to 10-min infusion [72]. The weekly schedule, which is considered a disadvantage for vinorelbine, is being evaluated for both paclitaxel [47-52] and docetaxel [73, 74], resulting in improved safety and tolerability profiles for the two taxanes. Other schedules of vinorelbine, such as the 96-h infusion, do not appear to offer an advantage over the weekly schedule [75].

Single-agent therapy in the elderly is emerging as a major role for vinorelbine. Vogel et al. [60] reported a 38% response rate in 56 women ≥60 years of age; an additional 16% experienced stable disease for greater than six months for an overall clinical benefit rate of 54%. In 31 women ≥65 years of age, Buonadonna et al. [76] reported overall response rates of 66% for first-line treatment and 26% for patients who had previously received chemotherapy for metastatic disease. Vinorelbine was extremely well tolerated by elderly patients in both trials. Vogel et al. [77] studied the subjective tolerability of single-agent vinorelbine in 221 patients stratified for age greater or less than 65 years. Toxicity was similar for older and younger patients, with very few grade 3 or 4 subjective side effects, regardless of age. Grade 3 asthenia (15% versus 8%) and constipation (6% versus 3%) occurred slightly more often in the older patients. Less than 15% of all patients reported alopecia; none of the cases were severe. The major side effect, regardless of age, was neutropenia, with similar rates of hospitalizations between younger and older patients (9% and 10%, respectively).

Docetaxel

Docetaxel’s (Taxotere®) chemical configuration and pharmacologic properties invite comparison with the older taxane, paclitaxel. Docetaxel was originally developed from a renewable resource, the needles of Taxus baccata, and esterified with a chemically synthesized side chain. Docetaxel is formulated in polysorbate 80 (Tween 80®) and alcohol rather than in polyoxyethylated castor oil (Cremophor®), which has been implicated in the hypersensitivity reactions associated with paclitaxel. Additional differences are docetaxel’s greater potency in cell lines and explanted human tumor cell, higher intracellular accumulation, higher binding to and slower dissociation from microtubules, and slower efflux from tumor cells [78-80].

First-Line Monotherapy

Phase II trial results show that response rates for first-line docetaxel 100 mg/m² consistently approach 60% (Table 5) [81-86], which appear to exceed the first-line response rates for 3-h and 24-h infusions of paclitaxel at doses <250 mg/m² and, possibly, weekly vinorelbine (Tables 1 and 3). The response rates for docetaxel were slightly lower at 75 mg/m² [84, 87] than at 100 mg/m².

Phase III data provide indirect evidence that docetaxel may be superior to paclitaxel. Chan et al. [85] reported that docetaxel 100 mg/m² every three weeks by 1-h infusion produced a response rate of 58%, which confirmed phase II results and was quantitatively higher than the 44% response rate of doxorubicin 75 mg/m²; however, this difference was

| Table 5. Docetaxel activity as a first-line, single agent in metastatic breast cancer |
|---|---|---|---|
| Dose, mg/m² | n of patients | Response rate, % | Authors [reference] |
| 100 | 37 | 68 | Chevallier et al., 1995 [84] |
| 100 | 37 | 68 | Fumoleau et al., 1996 [82] |
| 100 | 32 | 63 | Krakowski et al., 1995 [83] |
| 100 | 55 | 58 | Trudeau et al., 1996 [84] |
| 100 | 37 | 54 | Chan et al., 1997* [85] |
| 75 | 40 | 52 | Hudis et al., 1996 [86] |
| 75 | 15 | 40 | Dieras et al., 1994 [87] |

*Data updated from meeting abstract.
not significant in the subset that received first-line therapy after failing adjuvant alkylating therapy. When all patients were considered, including those who failed alkylating therapy for advanced disease, docetaxel induced higher response rates than doxorubicin (48% versus 33%; \( p = .008 \)). There was no difference between the two drugs in time to disease progression or survival duration [85]. In contrast, paclitaxel 200 mg/m\(^2\) by 3-h infusion was inferior to doxorubicin 75 mg/m\(^2\) as measured by response rate (25% versus 41%; \( p = .003 \)) and time to progression (4.1 versus 7.3 months; \( p = .0001 \)), but there was no difference in survival time [33]. Of course, determination of the relative activity of paclitaxel and doxorubicin may have been confounded by the dose and schedule of paclitaxel used in the previous trial. Ongoing phase III trials are clearly needed to determine which taxane is superior as first-line monotherapy for metastatic breast cancer.

**Second-Line Monotherapy**

Docetaxel was initially approved in the United States on the basis of its efficacy in patients with anthracycline-resistant tumors, but is now approved after failure of any chemotherapy. Response rates for second-line docetaxel ranged from 30% to 57% (Table 6) [85, 88-99]. Some of the lowest response rates were attributable to the use of doses <100 mg/m\(^2\) in Japan [97, 99] and Europe [98]. Nabholtz et al. [96] also reported lower response rates; however, this randomized trial established the superiority of single-agent docetaxel over the commonly used salvage regimen of mitomycin C and vinblastine in terms of response rate (30% versus 12%; \( p < .0001 \)), time to progression (19 versus 11 weeks; \( p = .001 \)) and, most importantly, overall survival time (median 11.4 versus 8.7 months; \( p = .0097 \)).

Additional efficacy information is available from compassionate-use or extended-access trials involving extensively pretreated patients. Trandafir et al. [100] reported an overall response rate of 19% in 241 patients who had received up to five previous chemotherapy regimens. Alexandre et al. [101] reported objective responses or SD in 61% of 886 women who had received an average of two prior chemotherapy regimens. Leonard et al. [102] reported a 57% overall response rate with docetaxel 100 mg/m\(^2\) and 34% with 75 mg/m\(^2\) doses. Another interesting report from Valero et al. [103] suggested that docetaxel was active in a small series of patients with paclitaxel-resistant cancer.

Docetaxel appears to be one of the most effective drugs in patients with liver metastases (Table 7) [81, 84, 85, 88, 91, 98, 100]. Chan et al. [85] reported that docetaxel produced a higher response rate than doxorubicin in patients with liver metastases (54% versus 27%; \( p < .001 \)). As well, Nabholtz et al. [96] observed greater efficacy with docetaxel versus mitomycin and vinblastine in patients with liver metastases whose disease progressed despite prior anthracycline-containing chemotherapy (33% versus 7%; \( p < .001 \)). Ironically, the prescribing information for docetaxel indicates that it should “generally not be given” if the bilirubin is greater than the upper limit of normal or if the serum glutamic-oxaloacetic transaminase and/or serum glutamate pyruvate transaminase is 1.5 times the upper limit of normal, concomitant with an

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**Table 6. Docetaxel activity as a second-line, single agent in metastatic breast cancer**

<table>
<thead>
<tr>
<th>Dose, mg/m(^2)</th>
<th>( n ) of patients</th>
<th>Anthracycline-pretreated patients, %</th>
<th>Response rate, %</th>
<th>Authors [reference]</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>35</td>
<td>100</td>
<td>57</td>
<td>Ravdin et al., 1995 [88]</td>
</tr>
<tr>
<td>100</td>
<td>46</td>
<td>100</td>
<td>54</td>
<td>Bonnetterre et al., 1997 [89]</td>
</tr>
<tr>
<td>100</td>
<td>13</td>
<td>NS</td>
<td>54</td>
<td>Vorobiof et al., 1996 [90]</td>
</tr>
<tr>
<td>100</td>
<td>34</td>
<td>100</td>
<td>53</td>
<td>Valero et al., 1995 [91]</td>
</tr>
<tr>
<td>100*</td>
<td>18</td>
<td>100</td>
<td>50</td>
<td>Terzoli et al., 1998 [92]</td>
</tr>
<tr>
<td>100</td>
<td>228</td>
<td>0</td>
<td>42</td>
<td>Chan et al., 1997** [85]</td>
</tr>
<tr>
<td>100</td>
<td>97</td>
<td>100</td>
<td>42</td>
<td>Sjöström et al., 1998 [93]</td>
</tr>
<tr>
<td>100</td>
<td>19</td>
<td>100</td>
<td>37</td>
<td>Vici et al., 1998 [94]</td>
</tr>
<tr>
<td>100</td>
<td>57</td>
<td>100</td>
<td>34</td>
<td>VanOosterum et al., 1996 [95]</td>
</tr>
<tr>
<td>100</td>
<td>203</td>
<td>100</td>
<td>30</td>
<td>Nabholtz et al., 1998 [96]</td>
</tr>
<tr>
<td>60</td>
<td>85</td>
<td>NS</td>
<td>44</td>
<td>Taguchi et al., 1994 [97]</td>
</tr>
<tr>
<td>50</td>
<td>83</td>
<td>63</td>
<td>34</td>
<td>Piccart et al., 1997 [98]</td>
</tr>
<tr>
<td>60*</td>
<td>10</td>
<td>100</td>
<td>30</td>
<td>Tominaga and Suzumura, 1998 [99]</td>
</tr>
</tbody>
</table>

*Docetaxel as ≥ third-line chemotherapy in >50% of patients.

**Data updated from meeting abstract.

NS = not stated.

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alkaline phosphatase level greater than 2.5 times the upper limit of normal. These guidelines were developed because such patients had a 25% decrease in docetaxel clearance and increased risk of severe toxicities [104]. Phase I trials are under way to establish “safe” doses of docetaxel in this setting. In the meantime, the dose of docetaxel should be reduced in patients with altered liver function, although the degree of reduction is still uncertain, and hematologic monitoring should be performed more frequently.

Safety

Docetaxel’s safety pattern has been the subject of much concern and debate. As with paclitaxel, profound granulocytopenia is common with docetaxel at 100 mg/m². The nadir appears early, on days 5 to 7, but the duration is relatively short; hence, the rate of infectious complications remains low. More troubling has been the fluid retention that appears with increasing duration of treatment [105] and is manifested by pedal edema and serious effusions. This problem has been circumvented with the use of steroid premedication [98]. Ravdin et al. [106] initially recommended five days of dexamethasone beginning the day before treatment; however, a three-day regimen may be as effective [107]. Now that fluid retention is no longer a serious problem, docetaxel will probably be used more frequently for the management of breast cancer.

Combination Chemotherapy with Taxanes or Vinorelbine

An exhaustive review of all possible combinations of available drugs is beyond the scope of this review, but some observations should be noted. Combinations of doxorubicin, with or without cyclophosphamide, and a taxane have been so effective in metastatic disease [108-114] that taxanes have entered clinical trials as adjuvant therapy. Henderson et al. [115] recently reported the early results of a trial suggesting that the sequence of doxorubicin and cyclophosphamide followed by paclitaxel may be superior to doxorubicin plus cyclophosphamide alone; however, the paclitaxel-doxorubicin combination may increase the frequency of stomatitis, myelosuppression [116], and cardiotoxicity [108, 110, 117, 118] because of sequence-dependent pharmacokinetic interactions between doxorubicin and paclitaxel given as a short (3-h) infusion. Results of other studies combining these two agents have not shown an increase in cardiotoxicity [109, 111, 112, 119]. Regardless, combination of these two drugs requires careful scheduling [120], which could reduce the amount of doxorubicin delivered. In contrast, there is no apparent pharmacokinetic interaction between docetaxel and doxorubicin [113, 114] and no evidence of increased cardiotoxicity compared with conventional anthracycline-containing regimens.

Vinorelbine has also been evaluated in combination regimens. Synergy between taxanes and vinorelbine observed in preclinical trials prompted many clinical trials [121-132] which yielded encouraging results. Vinorelbine combined with doxorubicin also produced good response rates, although doxorubicin causes universal alopecia [133-135]. Replacement of doxorubicin may lead to even more tolerable combinations, such as vinorelbine plus epirubicin [136-138], mitoxantrone [139, 140], losoxantrone, or liposomal doxorubicin [141].

Because of its excellent subjective safety profile and lack of alopecia, vinorelbine is being combined with other well-tolerated agents. Good response rates have been achieved with vinorelbine and fluorouracil [89, 142-145]. Drugs that could ultimately replace continuous-infusion fluorouracil, such as capecitabine, UFT (uracil and tegafur), or GW 776C85 plus oral fluorouracil, should be or are being tested. The combination of vinorelbine with another well-tolerated

<table>
<thead>
<tr>
<th>Dose mg/m²</th>
<th>n of prior chemotherapy regimens for metastases</th>
<th>n of responses/ n of evaluable patients (%)</th>
<th>Authors [reference]</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>0</td>
<td>12/16 (75)</td>
<td>Chevallier et al., 1995 [81]</td>
</tr>
<tr>
<td>100</td>
<td>0-1</td>
<td>40/70 (57)</td>
<td>Chan et al., 1997** [85]</td>
</tr>
<tr>
<td>100</td>
<td>1</td>
<td>15/27 (56)</td>
<td>Trudeau et al., 1996 [84]</td>
</tr>
<tr>
<td>100</td>
<td>1-2</td>
<td>4/12 (33)</td>
<td>Valero et al., 1995 [91]</td>
</tr>
<tr>
<td>100</td>
<td>1-2</td>
<td>34/102 (33)</td>
<td>Ravdin et al., 1995 [88]</td>
</tr>
<tr>
<td>50</td>
<td>1</td>
<td>34/102 (34)</td>
<td>Nabholtz et al., 1998 [96]</td>
</tr>
<tr>
<td>70 or 100</td>
<td>0-4</td>
<td>NS (19)</td>
<td>Piccart et al., 1997 [98]</td>
</tr>
</tbody>
</table>

*Most patients had normal liver function tests.
**Data updated from meeting abstract.
***Compassionate use trial.
NS = not stated.
drug, gemcitabine, is promising in lung cancer [146, 147] and is being evaluated in clinical trials of patients with breast cancer.

Finally, the new monoclonal antibody, trastuzumab, increased the activity of paclitaxel in women whose tumors overexpress HER2 in a randomized, phase III trial [148]. This finding, which is addressed later in this review, suggests that new therapeutic options will be incorporated into combination regimens in the near future.

LIPOSOMAL-ENCAPSULATED ANTHRACYCLINES

Several liposomal-encapsulated compounds which have been established as effective, safe, and tolerable in patients with AIDS-related Kaposi’s sarcoma [149] are being evaluated in patients with breast cancer. Stewart and Harrington [150] demonstrated that doxorubicin hydrochloride liposome injection (Doxil®) has prolonged circulation and localizes to tumor tissue. The slow release of doxorubicin mimics continuous-infusion schedules [151] and consequently decreases the usual acute toxicities associated with anthracyclines, such as nausea, vomiting, myelosuppression, vesicant properties, and alopecia [152]. Reduced cardiotoxicity has also been observed. In contrast, new toxicities may appear and, depending on the doses and schedules used, mimic those caused by continuous-infusion schedules of other drugs, such as stomatitis, diarrhea, and palmar-plantar erythrodyssplasia [149].

Reported results of Doxil in metastatic breast cancer have been sparse but encouraging [153-156]. Doxil is being evaluated in combination with paclitaxel [117], vinorelbine [141], cyclophosphamide [157], or docetaxel [158]. In fact, reduced cardiotoxicity has been reported for Doxil plus paclitaxel compared with doxorubicin and paclitaxel [117]. Another liposomal-encapsulated compound, TLC D-99, had equivalent efficacy compared with free doxorubicin in phase III trials [159] and reduced cardiotoxicity [160]. Breast cancer studies of liposomal-encapsulated daunorubicin are also in progress [161].

If comparative trials show that these liposome-encapsulated compounds have antitumor activity similar to that of doxorubicin, improved tolerability may encourage their use in place of the parent compound, either in combination or sequential regimens for the treatment of metastatic breast cancer, and ultimately in the adjuvant treatment of primary breast cancer. Delayed toxicity, however, may interfere with the ability to incorporate these compounds into dose-dense strategies.

LOSOXANTRONE

Losoxantrone is a new anthrapyrazole that appears to have increased activity compared with mitoxantrone and a similarly favorable subjective safety profile [162, 163]. As a single agent, losoxantrone was active in 43% [164] and 64% [165] of chemotherapy-naive patients, and in 30% [166] and 63% [165] of women with previously treated metastatic breast cancer. Combination regimens with cyclophosphamide and paclitaxel are being evaluated in clinical trials, which are closed to accrual. The preliminary response rate with combined losoxantrone and paclitaxel in patients with no prior chemotherapy for metastatic disease was 54% compared with 15% for single-agent paclitaxel [28]. If these results are maintained and cardiotoxicity is shown to be less than that with doxorubicin, losoxantrone, like the liposomal-encapsulated anthracyclines, could challenge doxorubicin as the most important new intercalator in breast cancer treatment.

GEMCITABINE

The pyrimidine nucleoside analogs, such as cytosine arabinoside, demonstrate considerable activity in hematologic malignancies but not in solid tumors [167]. Gemcitabine (Gemzar®) differs from cytosine arabinoside because it achieves higher concentrations and remains longer in tumor cells [168, 169]. Gemcitabine is indicated for the treatment of pancreatic carcinoma and has demonstrated a broad spectrum of antitumor activity against other solid tumors [167].

In trials of patients with breast cancer, gemcitabine produced a response rate of 35% in 14 chemotherapy-naive patients and 19% in 26 patients with one prior chemotherapy exposure [170]. Blackstein et al. [171] established a 37% response rate in chemotherapy-naive patients, whereas Possinger et al. [172] reported a disappointing 18% response rate using a dose and administration schedule similar to those in the preceding two studies. In previously treated patients, Spielmann et al. [173] reported a 28% response rate; however, lower doses produced very poor results in more heavily pretreated patients in an earlier trial conducted in the United States [174].

Gemcitabine clearly has activity in metastatic breast cancer, but the degree of activity needs to be clarified in further clinical trials. Its favorable subjective tolerability profile could make it an excellent palliative agent and a drug suitable for addition to existing combination regimens [175-179].

CONTINUOUS-INFUSION FLUOROURACIL AND NEWER ORAL SURROGATES

Fluorouracil, one of the oldest antineoplastic agents, has different safety and activity profiles depending on the administration schedule. For example, low-dose continuous infusions may have antitumor activity in patients who have failed bolus infusion [180]. Infusional fluorouracil is highly active in metastatic breast cancer [181-185], is widely used as salvage therapy in Europe, and is gaining popularity in the United States. It is especially useful in patients who have...
failed high-dose chemotherapy because infusional fluorouracil causes minimal myelosuppression. New oral agents have recently been synthesized to mimic the desirable features of a continuous-infusion schedule and to provide a less cumbersome method of delivery.

**Capecitabine**

Capecitabine (Xeloda®) is a thymidylate synthase inhibitor that serves as a pro-drug of fluorouracil. After oral administration and three enzymatic steps for activation, capecitabine produces plasma concentrations of fluorouracil that are comparable to those achieved after protracted continuous infusion of fluorouracil 300 mg/m²/d [186]. Capecitabine appears to produce high concentrations of fluorouracil selectively in tumor tissue in animal models [187] and in human colorectal liver metastases [188]. Capecitabine was recently approved by the FDA for paclitaxel-resistant breast cancer; the response rate is 20% in this setting [189]. Single-agent capecitabine compared favorably with CMF in older women with breast cancer [190] and against single-agent paclitaxel [44]. Additional studies are under way to evaluate combinations of capecitabine with paclitaxel [191], docetaxel [192], and liposomal-encapsulated daunorubicin.

**Uracil-Tegafur**

Tegafur is an established drug that has been used in Japan as an oral pro-drug to treat metastatic gastrointestinal cancer [193, 194] and, since 1991, as adjuvant therapy [195]. Adding uracil to tegafur increased antitumor activity [196], which led to the development of an oral compound containing tegafur and uracil in a molar ratio of 1:4 (UFT). Orally administered UFT resulted in higher peak plasma levels and a similar AUC compared with protracted i.v. infusion of fluorouracil [197].

Early reports of oral tegafur with or without leucovorin modulation in breast cancer revealed encouraging response rates [198-202]. UFT has been tested as salvage therapy in breast cancer patients [203]. UFT is being evaluated in combination regimens for metastatic breast cancer [204]. Oral UFT, intramuscular methotrexate, and oral leucovorin induced a 38% response rate in patients who had failed autologous stem cell transplantation [205].

**GW 776C85, a Dihydropyrimidine Dehydrogenase Inhibitor**

GW 776C85 is a potent inactivator of dihydropyrimidine dehydrogenase [206-208], the first enzyme in the degradative pathway of fluorouracil. Coadministration of GW 776C85 with fluorouracil confers the following advantages: increased bioavailability of oral fluorouracil, dramatically decreased effective dose of fluorouracil, and decreased myelosuppression resulting in a safety profile that is suitable for use in combination regimens.

GW 776C85 plus fluorouracil is being evaluated in patients with colorectal or head and neck cancers and is just beginning to be evaluated in patients with breast cancer. A preliminary response rate of 16% has been reported for this combination in patients with heavily pretreated breast cancer refractory to anthracycline and taxane therapy [209].

**Thymidylate Synthase Inhibitors and Folic Acid Antagonists**

Thymidylate synthase inhibitors merit consideration despite their more extensive evaluation in gastrointestinal than breast cancer. In addition to capecitabine, which has already been addressed, the two thymidylate synthase inhibitors being evaluated in patients with breast cancer are raltitrexed (Tomudex®) and LY 231514. Interim results of a phase II trial show that 31% of 36 patients with breast cancer responded to LY 231514, a multitargeted folic acid antagonist [210].

Edatrexate is a novel folic acid antagonist that has shown superior membrane transport and polyglutamation and increased activity in animal tumor models compared with methotrexate [211, 212], and displayed in vitro synergism with drugs such as paclitaxel and docetaxel [213]. Edatrexate has produced impressive response rates of 34% [214] and 41% [215] in phase II clinical trials as a single agent, but it has yet to be widely incorporated into combination chemotherapy regimens for breast cancer.

**Topoisomerase I Inhibitors**

Topoisomerase I inhibitors have been approved by the FDA for ovarian cancer (topotecan [Hycamtin®]) and colon cancer (irinotecan [Camptosar®]), but have not yet been widely studied in breast cancer [216]. The results of an older trial evaluating irinotecan [217] and two more recent trials with topotecan [218, 219] have not been overly encouraging, although some antitumor activity has been observed in patients with breast cancer.

**Trastuzumab, a Recombinant Monoclonal Antibody**

Trastuzumab (Herceptin®) is a recombinant humanized anti-p185HER2 monoclonal antibody (rHumAb HER2) that was recently approved for advanced breast cancer as single-agent therapy after failure of standard chemotherapy or in combination with paclitaxel as first-line therapy. Trastuzumab is only indicated for the 25% to 30% of women whose breast cancers amplify the HER2 oncogene, which is associated with overexpression of HER2 protein and was shown to correlate with poor clinical outcome.
The preliminary results of two large-scale clinical trials are impressive. Trastuzumab produced a 15% response rate with a median duration of response of 9.4 months in 222 patients previously treated with one or two prior chemotherapy regimens [220], which compares favorably with the duration of response associated with paclitaxel [28, 29, 36, 39, 43] or vinorelbine [68, 69]. In fact, some of the responses to trastuzumab were quite durable and lasted more than two years in the large phase II trial. One patient, who was enrolled in an earlier trial and had soft tissue metastasis, remains in complete remission, having received the antibody for more than six years (Larry Norton, M.D., personal communication). In the other large-scale trial [148], adding trastuzumab to doxorubicin (and cyclophosphamide) or paclitaxel significantly improved the objective response rate (62% versus 36%; p < .01) and prolonged the time to disease progression (8.6 versus 5.5 months; p < .001) compared with chemotherapy alone.

Cardiotoxicity is an unexpected adverse effect of trastuzumab. The risk is greater in patients who receive the combination of doxorubicin, cyclophosphamide, and antibody compared with chemotherapy alone [148]. The pathogenesis of this interaction is poorly understood. Otherwise, the subjective safety profile has been favorable [148, 220]. Aside from fever and chills, which generally occur only with the first dose of drug, toxicities have been rare. Patient tolerability and acceptance have been excellent, because the antibody is not associated with alopecia, significant gastrointestinal problems, or myelosuppression.

CONCLUSIONS

New chemotherapeutic agents are challenging the role of established compounds in the treatment of metastatic breast cancer. Docetaxel is beginning to emerge as the most effective single agent for the treatment of metastatic breast cancer, potentially surpassing doxorubicin. Paclitaxel, at standard dose ranging up to 225 mg/m² over 3 h, appears to be less active than docetaxel, both as first-line therapy and in patients with anthracycline-resistant cancer. Answers to questions regarding whether the well-tolerated weekly administration of paclitaxel will be superior to the 3-h and 24-h schedules require maturation of ongoing clinical trials.

Vinorelbine is a very well-tolerated drug that is underutilized in the United States in patients with breast cancer, probably because of lack of FDA approval and the perception that it is inferior to paclitaxel. Phase II trials indicate that first-line vinorelbine is at least as effective as first-line paclitaxel at standard doses and schedules. Response rates in second-line chemotherapy appear to have overlapping confidence intervals. The primary differences between the two agents are their safety profiles. Vinorelbine appears to be associated with reduced alopecia and neurotoxicity compared with paclitaxel given by 3-h infusions every three weeks. On the other hand, weekly paclitaxel has less myelotoxicity and fewer infusion site reactions than vinorelbine.

Liposomal-encapsulated anthracyclines, losoxantrone, gemcitabine, capetitabine, UFT, GW 776C85 plus fluorouracil, raltitrexed, LY 231514, and edatrexate also have significant activity in metastatic breast cancer; but topoisomerase I inhibitors appear to be less active. Trastuzumab has unequivocal antitumor activity in women whose tumors overexpress the oncogene, both as a single agent and in combination with cytotoxic chemotherapy. Trastuzumab is likely to become an important new agent because of its activity and lack of subjective toxicity in most patients. Finally, combinations of the previously mentioned drugs with each other and with older, effective agents will most likely result in improved outcomes in metastatic breast cancer and, ultimately, in the adjuvant setting as we move into the 21st century.

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