Effective oral chemotherapy for breast cancer: pillars of strength

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Traditionally, anticancer therapy has been dominated by intravenous drug therapy. However, oral agents provide an attractive approach to chemotherapy and use of oral treatments is increasing. We discuss the benefits and challenges of oral chemotherapy from the perspectives of patients, healthcare providers and healthcare funders. Important issues include patient preference, efficacy, compliance, bioavailability, reimbursement, use in special patient populations, financial and staff time savings and flexibility of dosing. We review data for traditional oral agents (e.g. cyclophosphamide, methotrexate), newer oral chemotherapies (e.g. capecitabine), oral formulations of traditionally intravenous agents (e.g. vinorelbine, idarubicin) and new biologic agents under evaluation in breast cancer (e.g. tyrosine kinase inhibitors). Lastly, we review studies of all-oral combination regimens. The wealth of data available and the increasing use of oral agents in breast cancer suggest that many of the concerns and perceptions about oral therapy, including efficacy and bioavailability, have been overcome, and that oral therapy will play a major role in breast cancer management in the future in both the metastatic and adjuvant settings.

Key words: breast cancer, capecitabine, oral chemotherapy, vinorelbine

introduction

Cancer treatment has traditionally been dominated by intravenous drug therapy [1]. There has, however, been a steady increase in the number of oral anticancer agents available during recent years, offering obvious benefits in terms of convenience and ease of administration, as well as addressing patients’ preference for oral therapy [2–5]. It is estimated that one-quarter of all anticancer agents under development are oral agents [6]. Several agents that are already approved in a range of tumour types (e.g. capcitabine, erlotinib, gefitinib, imatinib, lapatinib, lenalidomide, thalidomide, sunitinib, sorafenib) and many others in development (e.g. vatalanib, satraplatin) are or will be available only as oral formulations. Novel approaches to drug delivery, such as the development of hydrophilic polymer carriers to deliver drugs to the gut [7], are likely to further increase the number of oral drugs available.

This review investigates the impact of the expanding range of oral agents on cancer treatment, focusing on issues that have previously prevented the use of oral agents in patients with cancer and the opportunities that oral therapy offers. Oral agents that are already available, or that are under clinical evaluation for the treatment of breast cancer, are profiled to illustrate the potential of oral chemotherapy in this patient group.

defining the ideal oral agent

the patient’s perspective

Several surveys have shown that most patients prefer oral to intravenous therapy [3, 4, 8]. Nevertheless, a minority of patients prefer intravenous therapy because they believe that oral therapy is less effective than intravenous treatment [5, 8, 9]. In a survey of 59 patients starting oral chemotherapy for advanced breast cancer, a small percentage of patients worried that oral chemotherapy was prescribed as a last resort [9]. Therefore these patients require robust efficacy data to be convinced of the full benefit of oral chemotherapy.

Concerns about compliance also lead to a preference for intravenous therapy in a small proportion of patients [8, 9]. Compliance may be reduced if patients have to swallow a large number of tablets every day and a maximum of 6–8 tablets per day has been suggested as acceptable [1]. Compliance is also influenced by the patient’s ability to follow the dosing schedule, which is related to the complexity of the regimen [10, 11]. A simple schedule is also important if the benefits of oral administration are not to be outweighed by demanding...
frequent dosing. An oral regimen that governs patients’ daily activities is likely to be disruptive or inconvenient to patients. Patients receiving tegafur plus uracil (UFT), which is taken three times daily, should not eat for the hour before and the hour after taking their tablets because food decreases systemic exposure to the active cytotoxic moiety of UFT [12]. This places an extra burden on patients to organize their mealtimes around treatment. Demanding monitoring may also lessen the appeal of oral therapy. Patients receiving oral vinorelbine require weekly monitoring of neutrophil counts and medical supervision before each drug intake because of the high risk of grade 3/4 neutropenia [13, 14].

Intravenous therapy has a considerable impact on patients’ lives. Patients spend a substantial amount of time travelling to, waiting for and receiving cancer care. This places a major burden on patients [15], which can be reduced with home-based therapy. This benefit may be particularly important for patients living in remote areas or far from an oncology clinic [4]. In the past, healthcare professionals may have believed they could best interpret therapeutic choices for their patients [16, 17], with a tendency to focus purely on medical requirements without taking into account the impact intravenous therapy may have on patients (e.g. convenience, impact on daily activities and time spent in or travelling to hospital).

Lastly, oral chemotherapy may reduce anxiety in patients who are afraid of injections or are worried about a risk of intravenously transmitted diseases [4, 5], and may be a more appropriate route of administration if venous access is problematic.

Availability of active oral drugs will not ensure their use. Patients need effective, patient-focused education about their therapy, such as written take-home information, diaries, guidelines for dose reduction in case of adverse events and side-effect support kits [18, 19]. This is particularly important in the initial stages of therapy. As well as improving the tolerability of treatment through effective side-effect management and easing patients’ concerns about personal compliance, these strategies ultimately enable patients to self-manage their treatment, giving them a greater sense of empowerment. The features of an ideal oral therapy from the perspectives of patients, healthcare professionals and healthcare funders are summarized in Table 1.

the healthcare professional’s perspective

Traditionally, oncologists have favoured intravenous drug therapy. Possible reasons for this preference include perceptions of efficacy, concerns over bioavailability and compliance, difficulties in special patient populations and reimbursement systems. Physicians may have a prejudice that anticancer agents are best given intravenously because this route is more effective and reliable than oral administration [1]. However, the availability of agents with proven efficacy as well as oral convenience is changing this perception. In a survey of 96 US oncologists, 82% stated that their key consideration in selecting an oral chemotherapy agent was efficacy at least equivalent to intravenous alternatives [20].

Bioavailability can be limited with oral administration, which has hampered the development of oral anticancer drugs [21]. For example, P-glycoprotein, which is highly expressed in the gut epithelium, substantially impedes oral uptake of several anticancer drugs, including paclitaxel. Low bioavailability has been reported for a number of oral agents, including oral vinorelbine (33%) [22], topotecan (35%) [23] and etoposide (40–75%) [24, 25]. Co-administration of GF120918, a breast cancer resistance protein (BCRP) and P-glycoprotein inhibitor, significantly increases systemic exposure to oral topotecan [26] and oral paclitaxel [27], although these approaches are still in development.

Variable bioavailability can also be problematic: the 30–44% variation in bioavailability with oral topotecan results in a higher incidence of neutropenia when given at the maximum tolerated dose compared with intravenous administration [28]. Pharmacokinetic studies from the 1980s demonstrated significant variation (0–40%) in the bioavailability of conventional 5-fluorouracil (5-FU) when given orally. This variation is seen in studies of different patients and in repeat studies of the same patient [29]. Variability in systemic exposure to etoposide is three times greater with oral versus intravenous administration, potentially leading to considerable variability in toxicities between patients [24]. Bioavailability of oral agents may also be affected by food intake [30], making precise administration scheduling critical. In clinical practice, these features of certain oral agents mean that toxicities can be unpredictable and can vary greatly between patients. While healthcare professionals with extensive experience of a particular agent are less likely to be challenged by these issues, for healthcare professionals with less or no experience with a given oral agent, these variations can be problematic.

Concerns about compliance (both underdosing and overdosing) are frequently expressed with oral chemotherapy [10, 11]. Physicians may prefer to prescribe intravenous chemotherapy in patients who are unlikely to reliably take their medicine according to the correct schedule, as it provides a better opportunity to monitor treatment [11, 19]. Generally, patients receiving oral chemotherapy for cancer are highly motivated to take their treatment [31–33], but poor rates of compliance have been documented. In a study reported in 1990 by Lebovits et al., 43% of breast cancer patients did not take their oral medication as prescribed [34]. However, in a more recent, large, randomized phase III trial, it was reported that 96% of patients always remembered to take their oral chemotherapy tablets [31]. For many patients, the knowledge that adherence may improve clinical outcomes may help them take their oral medication as directed, emphasizing the important role of medical professionals in educating patients [35].

At the other end of the compliance spectrum, overdosing may be an issue. Oral therapy can be continued in the presence of life-threatening toxicity unrecognized or ignored by the patient. This is rarely the case when the oncologist prescribes intravenous chemotherapy. Patient education concerning the importance of individual dose adjustment in the management of adverse events is critical. Patients must be reassured that efficacy will not be impaired if toxicities necessitate dose reduction, as overdosing can lead to increased potentially serious toxicity [36]. With some oral agents, such as chlorambucil, a lack of symptoms may result in patients
Benefits/C15

Results of a time and motion study in the UK suggest that shortages. Oncology nurse and pharmacist staffing shortages professional’s standpoint is the potential to alleviate staffing intravenous therapy.

chemotherapy agents [37]. Consequently, US physicians earn supervision) but does not provide coverage for dispensing administered by a physician (or under his/her direct injection or infusion of a covered drug or biologic when administration. For example, in the USA, Medicare pays for bias of reimbursement systems toward intravenous preference for intravenous over oral therapy is the unintended undertreatment, with potentially fatal outcomes [21].

recognize drug–drug interactions can lead to overdosing or medications must be taken into account, and the drug interaction profile of oral agents must be well characterized. Failure to recognize drug–drug interactions can lead to overdosing or undertreatment, with potentially fatal outcomes [21].

Another factor that has frequently driven a physician preference for intravenous over oral therapy is the unintended bias of reimbursement systems toward intravenous administration. For example, in the USA, Medicare pays for the injection or infusion of a covered drug or biologic when administered by a physician (or under his/her direct supervision) but does not provide coverage for dispensing or administering oral drugs, including covered oral chemotherapy agents [37]. Consequently, US physicians earn considerably less for administering oral treatment than intravenous therapy.

A major advantage of oral chemotherapy from a healthcare professional’s standpoint is the potential to alleviate staffing shortages. Oncology nurse and pharmacist staffing shortages pose a major problem in cancer care in several countries. Results of a time and motion study in the UK suggest that switching from intravenous to oral chemotherapy would allow a 7-fold increase in the number of patients treated [38]. Effective adoption of oral chemotherapy requires a major commitment to patient education, especially in patients beginning oral chemotherapy. The nursing time required for ongoing patient education and support, such as answering telephone calls from patients receiving oral chemotherapy, must not be neglected. However, these demands are unlikely to outweigh the savings made by replacing intravenous with oral therapy and ultimately implementation of oral chemotherapy may provide resource savings [39, 40].

Until relatively recently, few oral chemotherapy drugs were available and therefore lack of familiarity was a barrier to acceptance. Although many oral agents are now available, several, such as temozolomide, imatinib and bexarotene, are used only in limited indications, thereby preventing widespread, regular use and ‘hands-on’ experience.

the healthcare funder’s perspective

Differences in reimbursement systems are important considerations for healthcare funders as well as healthcare professionals. Some healthcare systems (e.g. US Medicare prior to 2004) do not reimburse for oral chemotherapy, often leading to a preference for intravenous over oral therapy. However, oral therapy potentially offers considerable financial savings compared with intravenous therapy. Studies of capecitabine have demonstrated that in several countries, substantial cost savings can be made when intravenous therapy is replaced with oral therapy [39–44]. A French analysis of patients with stage III colon cancer treated in a randomized phase III trial demonstrated that oral capecitabine provided savings of €7025 and €3569 per patient compared with the intravenous Mayo Clinic and de Gramont regimens, respectively, from the third-party payer perspective, as well as improving outcomes for patients [44]. An Italian analysis also demonstrated that capecitabine is the ‘dominant strategy’ in pharmacoeconomic terms, providing a saving from the Italian hospital perspective of €2234 per patient [42]. The higher costs of 5-FU/leucovorin administration far outweigh the higher drug cost of capecitabine.

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Table 1. Summary of oral therapy from the perspectives of patients, healthcare professionals and healthcare funders

<table>
<thead>
<tr>
<th>Needs</th>
<th>Patients</th>
<th>Healthcare professionals</th>
<th>Healthcare funders</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Convincing efficacy</td>
<td>Efficacy equivalent to intravenous options</td>
<td>Reimbursement reform in some countries</td>
</tr>
<tr>
<td></td>
<td>Few tablets</td>
<td>High and predictable bioavailability</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Simple schedule</td>
<td>Patient education tools</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Minimal monitoring/laboratory testing</td>
<td>Time for patient education/follow-up</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Effective education</td>
<td>Experience</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reimbursement reform in some countries</td>
<td></td>
</tr>
<tr>
<td>Benefits</td>
<td>No needles</td>
<td>Tailored/flexible dosing</td>
<td>Cost savings</td>
</tr>
<tr>
<td></td>
<td>Reduced travel/clinic time</td>
<td>Staffing savings</td>
<td>Staffing savings</td>
</tr>
<tr>
<td></td>
<td>Empowerment</td>
<td></td>
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</tr>
</tbody>
</table>

Continuing therapy despite potentially life-threatening toxicities.

A major advantage for healthcare professionals of oral over intravenous therapy is its flexibility and adaptability. There are numerous opportunities to withdraw or modify therapy within cycles of treatment in the event of toxicity, whereas intravenous treatment cannot be withdrawn after it has been administered. For example, during one cycle of capecitabine/docetaxel combination therapy for breast cancer, patients receive one intravenous dose of docetaxel, whereas there are two opportunities per day to modify the capecitabine dose for the first 2 weeks.

Patients with cancer often develop an underlying gastrointestinal motility disorder, which can be related to surgery, hormonal secretions from tumours or a side effect of chemotherapy [11]. Malabsorption syndrome and liver dysfunction are common, and may interfere with the pharmacology of orally administered agents. Patients with significant oropharyngeal disability or bowel obstruction are unsuitable for oral chemotherapy, as are geriatric patients with dementia [11]. As with intravenous therapy, concurrent medications must be taken into account, and the drug interaction profile of oral agents must be well characterized. Failure to recognize drug–drug interactions can lead to overdosing or undertreatment, with potentially fatal outcomes [21].

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Table 2. Summary of oral agents evaluated as monotherapy in phase II and III trials in advanced/metastatic breast cancer

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of patients</th>
<th>Anthracycline-pretreated⁹</th>
<th>Taxane-pretreated⁹</th>
<th>Age range (years)</th>
<th>Response rate (%)</th>
<th>Median time to progression (months)</th>
<th>Median overall survival (months)</th>
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<td>No</td>
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<td>4⁸</td>
<td>24</td>
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<td>25</td>
<td>Yes</td>
<td>No</td>
<td>37–71</td>
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<td>NR</td>
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<td>No</td>
<td>34–75</td>
<td>19</td>
<td>NR</td>
<td>NR</td>
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<td>Eniluracil/5-FU</td>
<td>84</td>
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<td>Yes</td>
<td>28–74</td>
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<td>2.3</td>
<td>9.3</td>
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<td>106</td>
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<td>No</td>
<td>31–77</td>
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<td>9.6</td>
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<td>S-1</td>
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<td>NR</td>
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<td>NR</td>
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<td>12.2</td>
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<td>15.9</td>
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<td>161³</td>
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<td>Yes</td>
<td>28–83</td>
<td>14</td>
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<td>11.6</td>
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<td>No</td>
<td>20–73</td>
<td>28</td>
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<td>9</td>
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<td>31–70</td>
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<td>7.4</td>
<td>11.8</td>
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<td>58</td>
<td>No</td>
<td>No</td>
<td>35–79</td>
<td>31</td>
<td>4.0</td>
<td>NR</td>
<td>Freyer et al. [74]</td>
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<td>Vinorelbine (60 escalating to 80 mg/m²)</td>
<td>62</td>
<td>No</td>
<td>No</td>
<td>38–74</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Depierre et al. [14]</td>
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<td>72</td>
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<td>NR</td>
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<td>NR</td>
<td>NR</td>
<td>Amadori et al. [75]</td>
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<td>0</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Frontini et al. [76]</td>
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<td>NR</td>
<td>65–84</td>
<td>4</td>
<td>4.7</td>
<td>NR</td>
<td>Baweja et al. [77]</td>
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<td>98</td>
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<td>No</td>
<td>63–94</td>
<td>24</td>
<td>4.1</td>
<td>NR</td>
<td>Winer et al. [78]</td>
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<td>28–85</td>
<td>11</td>
<td>2.5</td>
<td>9.9</td>
<td>Winer et al. [78]</td>
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<td>No</td>
<td>65–81</td>
<td>22</td>
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<td>17</td>
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<td>No</td>
<td>No</td>
<td>70–280</td>
<td>Trial stopped after three toxic deaths</td>
<td>NR</td>
<td>8.3</td>
<td>Freyer et al. [80]</td>
</tr>
<tr>
<td>Oral etoposide</td>
<td>27</td>
<td>No</td>
<td>NR</td>
<td>37–76</td>
<td>10</td>
<td>2</td>
<td>NR</td>
<td>Bontenbal et al. [81]</td>
</tr>
<tr>
<td>Oral etoposide</td>
<td>30</td>
<td>NR</td>
<td>NR</td>
<td>33–80</td>
<td>30</td>
<td>NR</td>
<td>NR</td>
<td>Saphner et al. [82]</td>
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<td>Oral etoposide</td>
<td>43</td>
<td>Yes</td>
<td>NR</td>
<td>27–73</td>
<td>35</td>
<td>NR</td>
<td>NR</td>
<td>Martin et al. [83]</td>
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<tr>
<td>Oral etoposide</td>
<td>21</td>
<td>No</td>
<td>No</td>
<td>36–69</td>
<td>33</td>
<td>NR</td>
<td>NR</td>
<td>Neskovic-Konstantinovic et al. [84]</td>
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<tr>
<td>Oral etoposide</td>
<td>30</td>
<td>NR</td>
<td>NR</td>
<td>27–75</td>
<td>19</td>
<td>2.5</td>
<td>NR</td>
<td>Atienza et al. [85]</td>
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<td>30</td>
<td>NR</td>
<td>Yes</td>
<td>29–81</td>
<td>4</td>
<td>NR</td>
<td>NR</td>
<td>Pusztai et al. [86]</td>
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<td>Oral paclitaxel + cyclosporin</td>
<td>29</td>
<td>Yes</td>
<td>NR</td>
<td>Median 50</td>
<td>52</td>
<td>6.5</td>
<td>16</td>
<td>Héligson et al. [87]</td>
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In the metastatic colorectal cancer setting, use of first-line oral capecitabine resulted in significantly fewer hospital visits for drug administration, fewer days spent in hospital for management of treatment-related adverse events and reduced requirement for expensive drugs (in particular fluconazole and 5-HT3 antagonists) to manage adverse events compared with intravenous therapy [39]. These benefits outweighed the increased need for unscheduled home care, daycare and office and telephone consultations with physicians required with capcitabine therapy, with the reduction in drug administration visits providing an estimated saving of €2300-5000 per patient, depending on the country. A Dutch cost-benefit analysis indicated that treating patients with capcitabine instead of the intravenous Mayo Clinic regimen resulted in cost savings per patient of €1610 as first-line therapy and €934 in the adjuvant setting [40].

In the metastatic colorectal cancer setting, use of first-line oral capcitabine resulted in significantly fewer hospital visits for drug administration, fewer days spent in hospital for management of treatment-related adverse events and reduced requirement for expensive drugs (in particular fluconazole and 5-HT3 antagonists) to manage adverse events compared with intravenous therapy [39]. These benefits outweighed the increased need for unscheduled home care, daycare and office and telephone consultations with physicians required with capcitabine therapy, with the reduction in drug administration visits providing an estimated saving of €2300-5000 per patient, depending on the country. A Dutch cost-benefit analysis indicated that treating patients with capcitabine instead of the intravenous Mayo Clinic regimen resulted in cost savings per patient of €1610 as first-line therapy and €934 in the adjuvant setting [40].

### Oral agents in breast cancer

Not all cytotoxic agents are suitable for oral administration. It is unlikely that intravenous use of antiproliferative cytotoxics, which are generally given as intermittent, short-term therapy, will change. Oral therapy is better suited to schedule-dependent agents (e.g. topoisomerase I inhibitors or fluoropyrimidines) or other agents that need to be taken daily for months or years (e.g. signal transduction inhibitors, antiangiogenic drugs, hormonal therapies). Both cyclophosphamide and methotrexate are established oral agents for patients with breast cancer, although their role is usually as part of a combination regimen, traditionally with intravenous drugs. With the introduction and evaluation of newer oral chemotherapies, there has been a clear shift towards more widespread use of oral agents. In a survey of US oncologists conducted in 2005, more than 80% reported that their use of oral agents had increased during the previous 2 years [20]. The most common reasons cited for the change were availability of highly targeted agents, better supporting data and expanded indications for existing oral therapies.

The oral fluoropyrimidine capecitabine is available commercially as monotherapy and as a component of combination regimens for breast cancer (with intravenous docetaxel in patients pretreated with anthracyclines and, in the USA, in combination with lapatinib in patients with human epidermal growth factor receptor 2 (HER2)-positive disease after treatment with trastuzumab, an anthracycline and a taxane). Oral chemotherapeutic agents currently under evaluation for breast cancer include oral formulations of idarubicin, etoposide and vinorelbine and the new oral agents

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of patients</th>
<th>Anthracycline-pretreated</th>
<th>Taxane-pretreated</th>
<th>Age range (years)</th>
<th>Response rate (%)</th>
<th>Median time to progression (months)</th>
<th>Median overall survival (months)</th>
<th>Reference</th>
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</thead>
<tbody>
<tr>
<td>DJ-927 (oral taxane)</td>
<td>33</td>
<td>Yes</td>
<td>No</td>
<td>Median 50</td>
<td>21</td>
<td>NR</td>
<td>NR</td>
<td>Chan et al. [88]</td>
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<td>Oral irinotecan</td>
<td>78</td>
<td>Yes</td>
<td>Yes</td>
<td>34–85</td>
<td>22</td>
<td>NR</td>
<td>NR</td>
<td>Vukelja et al. [89]</td>
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<td>Oral irinotecan</td>
<td>103</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
<td>14/23</td>
<td>1.9/2.8</td>
<td>8.6/9.7</td>
<td>Perez et al. [90]</td>
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<td>Gimatecan</td>
<td>41</td>
<td>Yes</td>
<td>Yes</td>
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<td>10</td>
<td>NR</td>
<td>NR</td>
<td>Mariani et al. [91]</td>
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<td>Rubitecan</td>
<td>16</td>
<td>Yes</td>
<td>Yes</td>
<td>35–73</td>
<td>0</td>
<td>3.6</td>
<td>8.9</td>
<td>Chedid et al. [92]</td>
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<td>Temozolomide</td>
<td>19</td>
<td>NR</td>
<td>NR</td>
<td>43–75</td>
<td>0</td>
<td>1.8</td>
<td>NR</td>
<td>Trudeau et al. [93]</td>
</tr>
<tr>
<td>Marinamart</td>
<td>179</td>
<td>Yes</td>
<td>Yes</td>
<td>33–84</td>
<td>NR</td>
<td>4.7</td>
<td>24.7</td>
<td>Sparano et al. [94]</td>
</tr>
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<td>Bexarotene (RXR-selective retinoid)</td>
<td>145</td>
<td>No</td>
<td>No</td>
<td>27–92</td>
<td>3</td>
<td>1.9–2.2</td>
<td>NR</td>
<td>Esteva et al. [95]</td>
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<tr>
<td>Lapatinib (HER2-positive)</td>
<td>40</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>30–35</td>
<td>NR</td>
<td>NR</td>
<td>Gomez et al. [96]</td>
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<tr>
<td>Lapatinib (HER2-positive)</td>
<td>45</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
<td>24</td>
<td>NR</td>
<td>NR</td>
<td>Iwata et al. [97]</td>
</tr>
<tr>
<td>Sunitinib malate</td>
<td>64</td>
<td>Yes</td>
<td>Yes</td>
<td>Median 51</td>
<td>11</td>
<td>NR</td>
<td>NR</td>
<td>Miller et al. [98]</td>
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<td>Tipifarnib (farnesyl transferase inhibitor)</td>
<td>76</td>
<td>No</td>
<td>No</td>
<td>32–82</td>
<td>10/14</td>
<td>3.2/2.9</td>
<td>15.1/10.4</td>
<td>Johnston et al. [99]</td>
</tr>
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<td>Sorafenib</td>
<td>23</td>
<td>Yes</td>
<td>Yes</td>
<td>37–70</td>
<td>5</td>
<td>2</td>
<td>NR</td>
<td>Moreno-Aspitia et al. [100]</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>50</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>2</td>
<td>1.8</td>
<td>NR</td>
<td>Bianchi et al. [101]</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>58</td>
<td>NR</td>
<td>NR</td>
<td>29–70</td>
<td>2</td>
<td>2</td>
<td>11.7</td>
<td>von Minckwitz et al. [102]</td>
</tr>
<tr>
<td>ZD6474</td>
<td>46</td>
<td>Yes</td>
<td>Yes</td>
<td>32–81</td>
<td>0</td>
<td>1.4</td>
<td>NR</td>
<td>Miller et al. [103]</td>
</tr>
</tbody>
</table>

*aMajority of patients.
*bTime to treatment failure.
*cPhase III trial.
*dAt 4 mg/m² dose.

5-FU, 5-fluorouracil; NR, not reported; RXR, retinoid X receptor; UFT, tegafur plus uracil.
methotrexate and 5-FU (CMF) as first-line therapy [68]. In activity in pretreated metastatic breast cancer [54–67, 70]. In normal tissue. Capecitabine exhibits high single-agent higher TP concentrations in tumour tissue compared with doxifluridine. Capecitabine is converted to 5-FU via a three-dehydrogenase inhibitor eniluracil, which enables oral efficacy in phase II trials [47, 48]. The dihydropyrimidine diarrhoea. Another treatment, UFT, has shown disappointing presystemic first-pass metabolism, resulting in dose-limiting tissue leads to activation of a proportion of the dose through present in higher concentrations in tumour tissue than normal [104]. Doxifluridine is converted to 5-FU by TP, which is demonstrated activity in metastatic breast and colorectal cancers and is widely used in China, Korea and Japan [104]. Doxifluridine is converted to 5-FU by TP, which is present in higher concentrations in tumour tissue than normal tissue [105]. However, the presence of TP in normal colorectal tissue leads to activation of a proportion of the dose through pre-systemic first-pass metabolism, resulting in dose-limiting diarrhoea. Another treatment, UFT, has shown disappointing efficacy in phase II trials [47, 48]. The dihydropyrimidine dehydrogenase inhibitor eniluracil, which enables oral administration of 5-FU, demonstrated only modest activity in patients with heavily pretreated breast cancer [49], but shows more promise as first-line therapy for advanced disease [51]. In Japan, a fourth oral fluoropyrimidine, S-1, is approved for treatment as gastric cancer, and has shown promise in breast cancer [52, 53]. However, it is not available in Europe or the USA.

The oral fluoropyrimidine capcitabine was rationally designed to overcome the partial first-pass metabolism of doxifluridine. Capcitabine is converted to 5-FU via a three-step enzymatic process, the third stage of which exploits higher TP concentrations in tumour tissue compared with normal tissue. Capcitabine exhibits high single-agent activity in pretreated metastatic breast cancer [54–67, 70]. In earlier treatment settings, a recently reported randomized phase III trial demonstrated a significant survival benefit with capcitabine versus classical oral cyclophosphamide, methotrexate and 5-FU (CMF) as first-line therapy [68]. In a randomized phase II trial the efficacy of capcitabine monotherapy was similar to that of paclitaxel in anthracycline-pretreated patients [65]. Capcitabine also appears well tolerated and active in patients with predominant liver metastases and severe hyperbilirubinaemia [106]. Pharmacoeconomic studies suggest that in pretreated patients with metastatic breast cancer, capcitabine monotherapy is more cost-effective than (intravenous) comparator therapies (e.g. infused 5-FU, gemcitabine or vinorelbine) [107, 108].

The safety profile of capcitabine is characterized by gastrointestinal toxicities and hand–foot syndrome, but a particularly low incidence of myelosuppression and alopecia. The unusual side effects of capcitabine necessitate patient and physician education in recognizing and managing unfamiliar side effects, such as hand–foot syndrome [109]. However, the rarity of neutropenia and the high single-agent activity provide a strong rationale for integrating capcitabine into combination regimes. Capcitabine has been successfully combined with several chemotherapeutic and biologic agents, most notably docetaxel and paclitaxel [110–113].

**oral formulations of intravenous drugs**

Oral formulations of several drugs that were previously administered intravenously have been developed, including vinorelbine, idarubicin and etoposide.

**oral vinorelbine**

Oral vinorelbine is rapidly absorbed, with a T_max of 0.75–1.4 hours [22, 114]. Bioavailability of soft-gelatine capsules, the third and most recent oral formulation of vinorelbine, is 33–43% [22, 114], with 38% inter-individual variability [114]. Low bioavailability may be attributed to both incomplete absorption and to a first-pass effect (intestinal and hepatic) [22]. Of note, vomiting within 3 hours after dosing does not appear to reduce absorption of oral vinorelbine [22].

Early studies of oral vinorelbine revealed difficulties in defining a dosing schedule that provides an optimal efficacy:toxicity balance. A 60 mg/m² dose failed to produce any responses in patients with advanced breast cancer, but at a dose of 80 mg/m², 62% of patients experienced grade 4 neutropenia [13]. A starting dose of 60 mg/m² was chosen for further development, with escalation to 80 mg/m² at the fourth cycle if tolerated [14]. Several studies of oral vinorelbine have shown disappointing efficacy, possibly related to difficulties in escalating the dose sufficiently before encountering significant toxicity. In other studies, this regimen has demonstrated moderate efficacy but is characterized by a high rate of neutropenia, the risk of which increases after dose escalation to 80 mg/m² [74]. Consequently close haematological monitoring is essential [14]. Unlike the intravenous formulation, oral vinorelbine is also associated with frequent nausea, vomiting and diarrhoea [14, 74], and prophylactic antiemetics are recommended [14].

**oral idarubicin**

Data for single-agent oral idarubicin are limited. A weekly schedule is not recommended in elderly patients with breast...
cancer because of a high toxic death rate [80], although a subsequent study suggested that low-dose idarubicin is feasible in women ≥65 years of age [79].

other chemotherapeutic agents

Oral etoposide is associated with relatively frequent grade 3/4 haematological toxicities. In low-risk patients who had not received chemotherapy for at least 1 year, oral etoposide yielded a 30% response rate but led to two treatment-related deaths in 30 patients treated in a phase II study [82]. Other studies have demonstrated response rates of 4–35% [81, 83–86].

In a population pharmacokinetic study evaluating oral paclitaxel, there was considerable inter-patient variability [115]. Oral paclitaxel analogues are in development but no single-agent clinical data are available. Preliminary data for the semi-synthetic oral taxane DJ-927 in anthracycline-pretreated breast cancer have recently been presented [88]. Small studies in breast cancer evaluating the oral camptothecins irinotecan, gimatecan and rubitecan have been reported, but efficacy appears to be limited when these agents are given as monotherapy [89–92]. Temozolomide may be valuable in patients with brain metastases, but the single published trial of temozolomide in a general population of patients with breast cancer yielded disappointing results [93]. Phase II and III single-agent data for these and other oral chemotherapeutic agents are summarized in Table 2.

targeted agents

Among the oral targeted agents, tyrosine kinase inhibitors are in the most advanced stages of clinical development.

Lapatinib, a selective inhibitor of epidermal growth factor receptor and HER2 tyrosine kinases, has demonstrated single-agent activity in phase II studies in patients with HER2-overexpressing tumours [96, 97]. The tyrosine kinase inhibitor sunitinib produced a modest response rate in heavily pretreated patients in a recent phase II trial [98]. Gefitinib demonstrated minimal single-agent activity and clinical trials are now focusing on combination regimens with intravenous therapy [116]. The optimal dosing schedule of tipifarnib in breast cancer is being defined, but activity in solid tumours has been rather disappointing [117].

all-oral combinations

Several all-oral regimens are under investigation in breast cancer (Table 3). Recently published preliminary results from a phase III trial showed that the addition of lapatinib to capecitabine significantly improved time to disease progression compared with capecitabine alone in patients with HER2-positive disease after progression on trastuzumab, although no significant survival benefit is yet apparent [60]. All-oral regimens of capecitabine plus oral vinorelbine also show promise [118–122, 132–134]. Other combinations attracting interest include capecitabine plus oral idarubicin [135], capecitabine plus oral cyclophosphamide [136], capecitabine/idarubicin/cyclophosphamide triple combination [124], and capecitabine plus tipifarnib [137]. Studies of metronomic therapy using an all-oral combination of cyclophosphamide and methotrexate suggest that this is an effective and minimally toxic approach [128–130]. In a large trial in patients with treated or untreated advanced breast cancer, low-dose oral
cyclophosphamide and methotrexate produced responses in 21% of patients and median overall survival of 18.2 months [128]. Objective response correlated with prolonged clinical benefit [138].

Traditionally in the neoadjuvant and adjuvant settings, the sole reason for using oral formulations of intravenous drugs has been to improve convenience, a benefit that is less apparent if the oral agent is then combined with intravenous therapy. However, there is a strong rationale for using oral agents that show high single-agent activity and thus broaden the choice of agents available in this setting. Numerous cooperative group and multinational trials are comparing older neoadjuvant regimens with capecitabine-based combinations or sequential regimens incorporating capecitabine. Capecitabine has also attracted interest as a component of chemoradiation in the neoadjuvant setting. Radiotherapy upregulates intratumoral TP concentrations and has demonstrated synergy with capecitabine in preclinical models [139]. In the clinical setting, the combination appears active and enables treatment duration to be shortened [140]. In the adjuvant setting, randomized trials are assessing the potential of capecitabine to replace 5-FU-based combination regimens, evaluating the addition of capecitabine to standard regimens and assessing single-agent capecitabine.

disclosures

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references


conclusions

The most important characteristic of a chemotherapeutic agent is its efficacy. Other characteristics of an ideal therapy include a simple administration schedule, good, reliable absorption, a predictable pharmacokinetic profile, good tolerability and a well-characterized drug interaction profile. Providing efficacy and tolerability are not compromised, oral chemotherapy can be attractive to patients because of the associated benefits in convenience, avoidance of visits to the clinic and impact on daily activities. Daily or more frequent dosing also provides numerous opportunities to modify the dose and effectively manage side effects.

Of the oral anticancer agents available or under clinical development, some clearly overcome the concerns held by oncologists regarding efficacy and bioavailability (e.g. addition of capecitabine to docetaxel improves survival in metastatic breast cancer) and have the potential to offer patients improved convenience and home-based therapy. Capecitabine is increasingly being used as an effective first-line oral monotherapy for metastatic breast cancer and capecitabine plus anti-HER2 therapy shows efficacy after trastuzumab in HER2-positive disease. In the adjuvant setting, depending on the adverse-event profile, oral therapy enables patients to return to normal as soon as possible or permits different approaches to therapy (shortening intensive therapy and allowing maintenance therapy). As well as offering numerous benefits to patients, oncologists, oncology nurses, pharmacists and healthcare providers, the development and refinement of currently available oral treatments for breast cancer and the introduction of new oral agents are likely to overturn previous perceptions of oral chemotherapy.


