The role of UFT in advanced gastric cancer

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Background: Advanced gastric cancer has a poor prognosis, with a relative 5-year survival rate of 7%–27%. Chemotherapy, which improves overall survival (OS) and quality of life, is the main treatment option. Although numerous regimens have been investigated, there is no standard treatment. Combination chemotherapy, however, is associated with a significant survival benefit compared with monotherapy and i.v. 5-fluorouracil (5-FU) is one of the most widely used agents. UFT (tegafur–uracil) has similar efficacy to continuous infusion 5-FU with improved tolerability and is more convenient for patients.

Design: The efficacy and safety of UFT in the treatment of advanced gastric cancer have been demonstrated in a number of phase II studies.

Results: UFT with leucovorin (folinic acid) monotherapy shows overall response rates (ORRs) of 16%–29% and median OS of 5.8 months. Combination of UFT with cisplatin, etoposide, or paclitaxel shows ORRs of 35%–51% and median OS of 8.3–10.1 months. UFT-based three-drug combinations show ORRs of 41%–57% and median OS of 8.6–15 months. UFT-based combinations have a good tolerability profile, particularly a low incidence of myelosuppression, mucositis, and hand–foot syndrome.

Conclusion: UFT represents a logical replacement for 5-FU in chemotherapy regimens for the treatment of advanced gastric cancer.

Key words: advanced gastric cancer, combination therapy, phase II study, tegafur, UFT, uracil
The role of chemotherapy in advanced gastric cancer

Chemotherapy is the main treatment option for patients with advanced disease. Median OS of 8–12 months has been reported in patients undergoing chemotherapy compared with 3–5 months for those treated with best supportive care [8, 10]. These results have been confirmed by a recent meta-analysis that showed a convincing 6-month survival advantage for chemotherapy compared with best supportive care [11]. In a study by Glimelius et al. [8], QoL was evaluated using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30. Chemotherapy improved or prolonged QoL compared with best supportive care. In the overall category, 14 (45%) chemotherapy patients were considered to have a favorable QoL outcome compared with 6 (20%) best supportive care patients (P < 0.05). In the best supportive care group, the favorable QoL outcome was attributed to chemotherapy in one patient, irradiation in one patient, the effects of steroids and other palliative efforts in one patient, and a naturally prolonged asymptomatic period in three patients. In the chemotherapy group, 17 (55%) patients had a prolonged symptom-free period or improved symptomatology without severe toxicity compared with six (20%) patients in the best supportive care group (P < 0.01).

Although a large number of chemotherapy regimens have been investigated in clinical trials, there is no standard treatment for advanced gastric cancer. Several drugs, including i.v. 5-FU, cisplatin, and doxorubicin, have shown good single-agent activity. Intravenous 5-FU remains one of the most widely used chemotherapy agents and has been the cornerstone of combination regimens such as FAM (5-FU, doxorubicin, and mitomycin C), FAMTX (5-FU, doxorubicin, and methotrexate), ELF (etoposide, LV, and 5-FU), DCF (docetaxel, cisplatin, and 5-FU), and ECF (epirubicin, cisplatin, and continuous infusion 5-FU) [12–21]. Combination chemotherapy has been shown to be associated with a statistically significant (P = 0.001) survival benefit compared with monotherapy in a meta-analysis of several clinical trials [11]. This corresponded to a small but clinically relevant 1–2 months mean average survival benefit [11].

This meta-analysis also showed that three-drug combinations have a significant survival benefit compared with two-drug combinations [11]. The mean average survival difference between three- and two-drug regimens was ~1–2 months. Three-drug combination neo-adjuvant treatment has also been shown to improve survival compared with surgery alone [12]. In a randomized trial comparing ECF with surgery alone in patients with operable gastroesophageal cancer, ECF decreased tumor size and stage and significantly improved progression-free survival (PFS) (P < 0.001) and OS (P = 0.009) [12].

The survival benefits associated with combination chemotherapy need to be weighed against the additional toxicity and deterioration in QoL. In the treatment of gastric cancer, the combination of cisplatin, epirubicin, LV, and bolus 5-FU (PELF) has been shown to be associated with more toxicity than the continuous infusion 5-FU regimen ECP and a higher rate of treatment-related deaths, 3.3% versus 0.6% for continuous infusion 5-FU, respectively (P = 0.028) [11, 13–15].

Oral fluoropyrimidines

In order to improve tolerability and patient convenience, as well as improve efficacy, oral alternatives to i.v. 5-FU have been developed. The three oral fluoropyrimidines, which are all 5-FU prodrugs, are UFT (tegafur–uracil), capecitabine, and S-1. UFT is a combination of tegafur, an oral prodrug of 5-FU that is metabolized to 5-FU primarily in the liver, and uracil, a natural substrate for the liver enzyme dihydropyrimidine dehydrogenase (DPD), in a 1 : 4 M ratio. Uracil competes with 5-FU for DPD, inhibiting its degradation and leading to higher intratumoral 5-FU levels [22]. Importantly, phosphorylation of 5-FU is not significantly suppressed by uracil [23]. S-1 is a combination of tegafur, the DPD inhibitor gimeracil, and potassium oxonate, which reduces the gastrointestinal side-effects of 5-FU. S-1 is currently only licensed for use in Japan and is in phase III clinical trials for advanced gastric cancer in other regions. Capecitabine is converted to 5-FU via a three-step enzymic process in the liver and tumor cells.

The efficacy of S-1 in the treatment of advanced gastric cancer has been demonstrated in several phase II trials with overall response rates (ORRs) of 26%–49% [7]. The main grade 3/4 toxic effects were hematologic, including leukopenia, granulocytopenia, and decreased hemoglobin and haematocrit, while the most common non-hematologic toxic effect was diarrhea [7]. The results of two phase III studies have been reported [24, 25]. In one phase III study, S-1 was well tolerated and showed significant noninferiority to 5-FU alone in terms of OS (11.4 versus 10.8 months) [24]. In another phase III study, S-1 plus cisplatin was effective and well tolerated and superior to S-1 alone in terms of OS (13.0 versus 11.0 months) and ORR (54% versus 31%) [25]. In these studies, the main grade 3/4 adverse events associated with S-1 monotherapy were decreased hemoglobin (13%), neutropenia (11%), anorexia (12%), and diarrhea (8%) [24, 25]. S-1 has also been shown to be effective and well tolerated as adjuvant therapy for locally advanced gastric cancer [26]. In a phase III clinical trial, the 3-year OS rate with S-1 was significantly greater than with surgery alone (80% versus 70%, P < 0.002) in east Asian patients [26]. The most common grade 3 adverse events were anorexia (6%), nausea (4%), and diarrhea (3%). Only one patient experienced a grade 4 adverse event of anorexia.

UFT has also been shown to be effective and well tolerated as adjuvant therapy for locally advanced gastric cancer in Japanese patients [27]. In this randomized study, the 5-year OS rate was 86% for UFT and 73% in the control group (P = 0.017). The most common grade 3 adverse events were neutropenia (13%), hyperbilirubinemia (9%), and anorexia (7%). Only one patient experienced a grade 4 adverse event of diarrhea.

Capecitabine has been shown to be effective as monotherapy and in combination for the treatment of advanced gastric cancer in a number of phase II studies with ORRs of 6%–34%.
and 17%–67%, respectively, and median OS of 8.1–10.0 months and 5.9–17.2 months, respectively [28–31].

Capecitabine monotherapy was generally well tolerated with a low incidence of grade 3/4 adverse events. The most frequent grade 3/4 adverse event was hand–foot syndrome (HFS), which was reported by 7%–13% of patients [29, 31]. Other common grade 3/4 adverse events were granulocytopenia (7%) and anorexia (8%) [29]. In a phase III study comparing capecitabine plus cisplatin with continuous infusion 5-FU plus cisplatin, median OS was 10.7 months and 9.5 months, respectively, showing the capecitabine combination was significantly noninferior (P = 0.0146) [32]. Capecitabine plus cisplatin was significantly superior to 5-FU plus cisplatin in terms of ORR: 41% versus 29% (P = 0.0295). Capecitabine was well tolerated: the most common treatment-related grade 3/4 adverse events were neutropenia (16%), vomiting (7%), and diarrhea (5%) [32]. Twenty-two percent of patients receiving capecitabine experienced HFS. Capecitabine has also been shown to be effective in the treatment of advanced esophageal cancer in a phase III study comparing capecitabine with fluorouracil and oxaliplatin with cisplatin (the REAL 2 trial) [33]. Patients were randomly assigned to one of four regimens: ECF, epirubicin plus oxaliplatin and fluorouracil (EOF), epirubicin plus cisplatin and capecitabine (ECX), or epirubicin plus oxaliplatin and capecitabine (EOX). Comparing ECF to EOF, ECX, and EOX, there were no significant differences in ORRs (41%, 42%, 46%, and 48%, respectively) and grade 3/4 non-hematologic toxicity (36%, 42%, 33%, and 45%, respectively).

While similar in many respects, the tolerability profiles of UFT and capecitabine differ in the incidence of HFS. HFS is very rare (<0.01%) observed in patients treated with UFT [34] but occurs in over half of all patients treated with capecitabine [35].

**rationale for replacing 5-FU with UFT**

Bolus i.v. 5-FU can result in significant toxic effects and continuous infusion requires portable infusion devices, which can lead to complications such as thrombosis and infection [36, 37], as well as being inconvenient for patients. The complications resulting from the central venous line, which is mandatory for continuous infusion 5-FU, occurred in 15% of ECF-treated patients in a study by Webb et al., while 16% of patients receiving the ECF regimen in a study by Ross et al. had exit-site infections and a further 7% experienced thrombosis [14, 15].

UFT has been shown to provide comparable pharmacokinetics with continuous infusion 5-FU in phase I and phase II studies [38–40]. Tegafur is well absorbed after oral administration, resulting in higher peak plasma levels of 5-FU and a similar area under the curve to those achieved with continuous infusion 5-FU [38, 39]. The main adverse events observed were diarrhea, nausea, and vomiting. The occurrence of these adverse events was significantly correlated with the plasma levels of 5-FU after oral administration of UFT [38, 39].

Studies have shown that patients prefer oral to i.v. therapy provided that efficacy is not compromised and that side-effects are not more frequent [41]. In three randomized phase II studies, two of which were cross over studies [40, 42], patients expressed a preference for oral treatment with UFT over i.v. 5-FU [40, 42, 43]. The main reasons for preferring UFT in these studies were the convenience of oral therapy and improved tolerability. Clinical studies in metastatic colorectal cancer (mCRC) have shown that UFT with LV has comparable efficacy to 5-FU/LV [44, 45]. Importantly, UFT with LV had a significantly better safety profile than 5-FU: the incidence of hematological malignancies was significantly lower in the UFT group, with fewer episodes of febrile neutropenia and documented infection. Notably, there was no evidence of severe grade 3/4 HFS with UFT.

UFT has similar efficacy to continuous infusion 5-FU and improved tolerability but does not have the inconvenience and associated side-effects of catheterization and portable infusion devices. UFT therefore represents a logical replacement for 5-FU in chemotherapy regimens for the treatment of advanced gastric cancer. Since three-drug regimens have been shown to be the most effective combination chemotherapy for advanced gastric cancer, in terms of ORR and OS [11], UFT-based three-drug combinations are the main focus of this review.

**UFT phase II clinical studies in advanced gastric cancer monotherapy**

UFT with LV monotherapy is effective and well tolerated in the treatment of advanced gastric cancer with response rates of 16%–29% and OS of 5.8 months reported in two trials [46, 47]. In one study, 16 patients received UFT 480 mg/m2/day in three divided doses and LV 25 mg/m2/day in four divided doses on days 1–21 of a 28-day cycle. Patients received a median of four cycles (range 1–9) [46]. The ORR was 29% [95% confidence interval (CI) 4.9% to 52.3%]: one of 14 assessable patients (7%) achieved a complete response (CR) and three (22%) a partial response (PR). Median OS was 5.8 months. The main grade 3/4 adverse events were diarrhea, nausea/vomiting, and oral mucositis. There were no severe infections or treatment-related deaths. In another study, 38 patients received UFT 300 mg/m2/day plus LV 90 mg/day, both in three divided doses, on days 1–28 of a 35-day cycle [47]. The ORR was 16% in 25 assessable patients, with one CR (4%) and three PRs (12%). The main grade 3/4 adverse events were diarrhea and nausea/vomiting. There were no treatment-related deaths. No HFS was reported in either study.

**combination therapy**

The main studies investigating the efficacy of UFT with LV plus one or more agents in the treatment of advanced gastric cancer are summarized in Table 1.

**Two-drug combinations.** UFT plus cisplatin: This combination was effective and well tolerated in two Japanese studies [48, 49]. In one study, 28 patients received UFT 400 mg/m2/day in two divided doses for 21 days and i.v. cisplatin 90 mg/m2 by 24-h continuous infusion 5–7 days after the start of UFT therapy in a 28-day cycle [48]. The dose of UFT was reduced to 250 mg/m2 after 8 weeks and the dose of cisplatin was reduced to 80 mg/m2 after the first cycle. Fourteen patients (50%) achieved a PR and...
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<tr>
<th>Author</th>
<th>No. of patients</th>
<th>Regimen</th>
<th>ORR (CR)</th>
<th>OS (months)</th>
<th>Grade 3/4 adverse events</th>
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<td><strong>Monotherapy</strong></td>
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<tr>
<td>Kim et al. [46]</td>
<td>16</td>
<td>UFT 480 mg/m²/day + LV 25 mg/m² day on days 1–21 every 28 days</td>
<td>29% (7%)</td>
<td>5.8</td>
<td>Diarrhea 44%, stomatitis/mucositis 13%, nausea/vomiting 13%</td>
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<tr>
<td>Ravaud et al. [47]</td>
<td>38</td>
<td>UFT 300 mg/m² day + LV 90 mg/day on days 1–28 every 35 days</td>
<td>16% (4%)</td>
<td>NR</td>
<td>Diarrhea 28%, nausea 11%, asthenia 11%</td>
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<td><strong>Combination therapy</strong></td>
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<td>Two-drug regimens</td>
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<tr>
<td>Suga et al. [48]</td>
<td>28</td>
<td>UFT: 400 mg/m²/day days 1–21; cisplatin: 90 mg/m² day 1 every 28 days</td>
<td>50% (0%)</td>
<td>10.1</td>
<td>Leukopenia 11%</td>
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<td>Sato et al. [49]</td>
<td>43</td>
<td>UFT: 400 mg/m²/day days 1–21; cisplatin: 80 mg/m² day 8 on every 28 days</td>
<td>51% (0%)</td>
<td>8.3</td>
<td>Neutropenia 22%, anemia 12%, leukopenia 10%, thrombocytopenia 10%, GOT/GPT increase 10%</td>
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<td>Feliu et al. [50]</td>
<td>46</td>
<td>UFT: 390 mg/m²/day days 1–14; LV: 500 mg i.v. day 1 30 mg/day days 2–14; etoposide: 100 mg/m² i.v. day 1, 200 mg/m² p.o. days 2 and 3 every 28 days</td>
<td>35% (9%)</td>
<td>9.0</td>
<td>Diarrhea 17%, anemia 13%, nausea/vomiting 11%</td>
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<td>Chao et al. [51]</td>
<td>55</td>
<td>UFT: 300 mg/m²/day + LV: 90 mg/day days 1–14; paclitaxel: 100 mg/m² days 1 and 8 every 21 days</td>
<td>50% (4%)</td>
<td>9.8</td>
<td>Neutropenia 45%, leukopenia 18%, diarrhea 13%</td>
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<td>Three-drug regimens</td>
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<td>Kim et al. [53]</td>
<td>37</td>
<td>UFT: 360 mg/m² day + LV 25 mg/m²/day days 1–21; cisplatin 60 mg/m² day 1; epirubicin: 50 mg/m² day 1 every 28 days</td>
<td>54% (5%)</td>
<td>10.0</td>
<td>Leukopenia 38%, nausea/vomiting 30%, stomatitis/mucositis 14%, thrombocytopenia 11%, diarrhea 11%</td>
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<td>Jeen et al. [54]</td>
<td>52</td>
<td>UFT: 360 mg/m² day + LV 45 mg/day days 1–21; cisplatin 60 mg/m² day 1; epirubicin: 50 mg/m² day 1 every 28 days</td>
<td>57% (6%)</td>
<td>15.0</td>
<td>Neutropenia 42%, nausea 27%, vomiting 17%, thrombocytopenia 14%</td>
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<td>Saglam [55]</td>
<td>19</td>
<td>UFT 300 mg/m²/day + LV 90 mg/day days 1–21; cisplatin 60 mg/m² day 1; epirubicin 50 mg/m² day 1 every 28 days</td>
<td>42% (16%)</td>
<td>14.0</td>
<td>Nausea/vomiting 21%</td>
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<td>Idelevich et al. [56]</td>
<td>39</td>
<td>UFT 300 mg/m²/day day 1 + LV 30 mg/m²/day days 1–22; cisplatin 60 mg/m² day 1; epirubicin: 50 mg/m² day 1 every 28 days</td>
<td>38% (5%)</td>
<td>9.5</td>
<td>Leukopenia 25%, neutropenia 20%</td>
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<td>Woo et al. [57]</td>
<td>35</td>
<td>UFT 300 mg/m² day 1–21; cisplatin 60 mg/m² day 1; epirubicin: 50 mg/m² day 1 every 21 days</td>
<td>41% (0%)</td>
<td>8.6</td>
<td>Nausea/vomiting 28%, leukopenia 25%</td>
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<tr>
<td>Oh et al. [58]</td>
<td>52</td>
<td>UFT: 400–600 mg/m²/day + LV: 75 mg/m²/day days 1–21; docetaxel: 60 mg/m² day 1; cisplatin: 75 mg/m² day 1 every 28 days</td>
<td>50% (8%)</td>
<td>11.2</td>
<td>Neutropenia 69%, nausea/vomiting 23%, diarrhea 17%</td>
</tr>
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UFT, tegafur–uracil; ORR, overall response rate; CR, complete response; OS, overall survival; NR, not reported; GOT/GPT, glutamic-oxaloacetic transaminase/glutamic-pyruvic transaminase.
median OS was 10.1 months. There were no grade 4 adverse events. Grade 3 leucopenia occurred in three (11%) patients. In a second study, 43 patients received UFT 400 mg/m²/day in two divided doses on days 1–21 of a 28-day cycle and i.v. cisplatin 80 mg/m² on day 8 [49]. The median number of cycles was 3 (range 1–8). The ORR was 51% (95% CI 35.0% to 67.2%) in 41 assessable patients, with 21 patients achieving a PR. Median OS was 8.3 months. The main grade 3/4 adverse events were neutropenia (22% of patients), anemia (12%), leucopenia (10%), thrombocytopenia (10%), and glutamic–oxaloacetic transaminase/glutamic-pyruvic transaminase increase (10%). No HFS was reported in either study.

UFT plus etoposide: This combination was found to be effective, well tolerated, and easy to administer in one study [50]. Forty-six patients received i.v. etoposide 100 mg/m² on day 1 and 200 mg/m² on days 2 and 3, UFT 390 mg/m²/day in two divided doses on days 1–14, and i.v. LV 500 mg/m² on day 1 followed by oral LV 15 mg/day in two divided doses on days 2–14 of a 28-day cycle [50]. Treatment was repeated every 28 days for a minimum of three cycles. The ORR was 35% (95% CI 22% to 51%): four patients (9%) achieved a CR and 12 (26%) a PR. Median OS was 9 months. The main grade 3/4 adverse events were diarrhea (17% of patients), anemia (13%), and nausea/vomiting (11%). Although grade 1/2 HFS was observed in three patients (7%), no severe (grade 3/4) HFS was reported.

UFT plus paclitaxel: This combination was effective, well tolerated, and convenient in a multicenter trial [51]. Fifty-five patients received paclitaxel 100 mg/m² on days 1 and 8, and UFT 300 mg/m²/day in three divided doses with oral LV 25 mg/m²/day in three divided doses with oral LV 25 mg/m²/day in three divided doses with oral LV 25 mg/m²/day in three divided doses with oral LV 25 mg/m²/day in three divided doses with oral LV 25 mg/m²/day in three divided doses with oral LV 25 mg/m²/day in three divided doses with oral LV 25 mg/m²/day in three divided doses with oral LV 25 mg/m²/day in three divided doses with oral LV 25 mg/m²/day in three divided doses with oral LV 25 mg/m²/day in three divided doses with oral LV 25 mg/m²/day in three divided doses with oral LV 25 mg/m²/day in three divided doses with oral LV 25 mg/m²/day in three divided doses with oral LV 25 mg/m²/day in three divided doses with oral LV 25 mg/m²/day in three divided doses with oral LV 25 mg/m²/day in three divided doses with oral LV 25 mg/m²/day in three divided doses with oral LV 25 mg/m²/day in three divided doses with oral LV 25 mg/m²/day in three divided doses with oral LV 25 mg/m²/day in three divided doses with oral LV 25 mg/m²/day in three divided doses with oral LV 25 mg/m²/day in three divided doses with oral LV 25 mg/m²/day in three divided doses with oral LV 25 mg/m²/day in three divided doses with oral LV 25 mg/m²/day in three divided doses with oral LV 25 mg/m²/day in three divided doses with oral LV 25 mg/m²/day in three divided doses with oral LV 25 mg/m²/day in three divided doses with oral LV 25 mg/m²/day in three divided doses with oral LV 25 mg/m²/day in three divided doses with oral LV 25 mg/m²/day in three divided doses with oral LV 25 mg/m²/day in three divided doses with oral LV 25 mg/m²/day in three divided doses with oral LV 25 mg/m²/day in three divided doses with oral LV 25 mg/m²/day in three divided doses with oral LV 25 mg/m²/day in three divided doses with oral LV 25 mg/m²/day in three divided doses with oral LV 25 mg/m²/day in three divided doses with oral LV 25 mg/m²/day in three divided doses with oral LV 25 mg/m²/day in three divided doses with oral LV 25 mg/m²/day in three divided doses with oral LV 25 mg/m²/day in three divided doses with oral LV 25 mg/m²/day in three divided doses with oral LV 25 mg/m²/day in three divided doses with oral LV 25 mg/m²/day in three divided doses with oral LV 25 mg/m²/day in three divided doses with oral LV 25 mg/m²/day in three divided doses with oral LV 25 mg/m²/day in three divided doses with oral LV 25 mg/m²/day in three divided doses with oral LV 25 mg/m²/day in three divided doses with oral LV 25 mg/m²/day in three divided doses with oral LV 25 mg/m²/day. In a study by Jeen et al. [54], 52 patients received a similar regimen with the same doses of epirubicin, cisplatin, and UFT but a higher dose of LV than used in the Kim et al. study: i.v. epirubicin 50 mg/m² and i.v. cisplatin 60 mg/m² on day 1 and UFT 360 mg/m²/day with LV 45 mg/day in three divided doses on days 1–21 of a 28-day cycle. Patients received a median of five cycles (range 1–10). In 47 assessable patients, the ORR was 57% (95% CI 71.5% to 43.3%): three patients (6%) achieved a CR and 24 a PR (51%). SD was reported in 11 patients (23%). Median OS was 15 months (range 2–33+). The main grade 3/4 adverse events were neutropenia in 22 patients (42%), nausea in 14 (27%), vomiting in nine (18%), and thrombocytopenia in seven (14%) patients. No HFS was reported. There were no severe infections or treatment-related deaths.

Two more recent studies investigated a lower 300 mg daily dose of UFT [55, 56]. In a study by Saglam [55], 19 chemotherapy-naive patients received i.v. epirubicin 50 mg/m² and i.v. cisplatin 60 mg/m² on day 1 and UFT 300 mg/m²/day with LV 90 mg/day on days 1–21 of a 28-day cycle. The median number of cycles was 3 (range 1–6). The ORR was 42%: three patients (16%) achieved a CR and five (26%) a PR. Three patients (16%) had SD. Median OS was 14 months. The main grade 3 adverse events were nausea/vomiting in four (21%) patients, diarrhea in one (5%), and hemoglobin toxicity in one (5%) patient. No grade 4 diarrhea, nausea, or vomiting was observed. No HFS was reported. In a study by Idleieivich et al. [56], 39 patients received i.v. epirubicin 50 mg/m² and i.v. cisplatin 60 mg/m²/day on day 1 plus UFT 300 mg/m²/day with oral LV 30 mg/m²/day in two divided doses on days 1–22 of a 28-day cycle. Patients received a median of five cycles of treatment (range 2–8). All patients were assessable for efficacy and safety. The ORR was 38% (95% CI 24% to 52%): two patients (5%) achieved a CR and 13 (33%) a PR. Sixteen patients (41%) had SD. Median OS was 9.5 months (range 8.5–13.5). The main grade 3/4 adverse events were leucopenia in 10 (25%) patients, neutropenia in eight (20%), diarrhea in three (8%), and nausea/vomiting in three (8%) patients. No HFS was reported. There were no treatment-related deaths.

Woo et al. [57] assessed a 21-day regimen of i.v. epirubicin 50 mg/m² and i.v. cisplatin 60 mg/m² on day 1 and UFT 300 mg/m²/day in three divided doses without LV or a rest period between cycles. The median number of cycles was 4 (range 2–10). Thirty-five patients were included and 32 were assessable: the ORR was (41%), all 13 patients achieving a PR. Ten patients (31%) had SD. Median OS was 8.6 months. Grade 3/4 leucopenia was reported in eight (25%) patients. Grade 3 adverse events included nausea/vomiting in nine (28%) patients and thrombocytopenia in three (9%). Three patients (9%) experienced grade 1/2 HFS. No grade 3/4 diarrhea was observed. There were no treatment-related deaths.

UFT, docetaxel, and cisplatin: In a study of first-line treatment, 52 patients received i.v. docetaxel 60 mg/m² for 1 h followed by i.v. cisplatin 75 mg/m² for 2 h on day 1 and UFT
400–600 mg/m²/day with LV 75 mg/m²/day in three divided doses on days 1–21 of a 28-day cycle [58]. The combination was effective and had an acceptable tolerability profile. The ORR was 30% (95% CI 26.4% to 33.6%); four patients achieved a CR (8%) and 22 a PR (42%). Seventeen patients (33%) had SD. Median OS was 11.2 months (range 4–156+). The main grade 3/4 adverse events were neutropenia in 36 patients (69%), nausea/vomiting in 12 patients (23%), diarrhea in nine patients (17%), mucositis in three patients (6%), and thrombocytopenia in three patients (6%). No HFS was reported. There were no treatment-related deaths.

In contrast, docetaxel in combination with cisplatin and 5-FU (DCF) has been shown to be associated with increased hematologic toxicity compared with cisplatin plus 5-FU (CF) [18]. Treatment-related grade 3/4 adverse events occurred in 69% of patients receiving DCF versus 59% of patients receiving CF. Grade 3/4 neutropenia (82% versus 57%), leukopenia (65% versus 31%), and all-grade complicated neutropenia (febrile neutropenia or neutropenic infection: 29% versus 12%) were significantly more frequent in patients receiving DCF than CF ($P < 0.05$). In patients aged 65 years or older, grade 3/4 treatment-related infection was more frequent with DCF (20%) than CF (9%).

### new combinations with targeted therapy

The combination of chemotherapy plus a targeted therapeutic agent is a promising new area for the treatment of advanced gastric cancer and several combination regimens are being investigated, such as irinotecan plus cisplatin plus bevacizumab and FOLFIRI plus cetuximab, with encouraging response rates, OS, and acceptable toxicity [59, 60]. In a phase II study, 47 patients with metastatic or unresectable gastric/ gastroesophageal junction adenocarcinoma received bevacizumab 15 mg/kg on day 1 and irinotecan 65 mg/m² and cisplatin 30 mg/m² on days 1 and 8, every 21 days [59]. Among 34 assessable patients, the ORR was 65% (95% CI 46% to 80%), with 20 patients (59%) achieving a PR and two patients (6%) a CR. Twelve patients had SD. Median OS was 12.3 months. There was no increase in chemotherapy-related toxicity. Possible bevacizumab-related adverse events included grade 3 hypertension in 13 patients (28%), gastric perforation in two patients (4%) and near perforation in one patient (2%), and myocardial infarction in one patient (2%). Grade 3/4 thromboembolic events occurred in 12 patients (25%).

In another phase II study, 38 previously untreated patients with confirmed advanced gastric/gastroesophageal adenocarcinoma received i.v. cetuximab at an initial dose of 400 mg/m² followed by weekly doses of 250 mg/m², i.v. irinotecan 180 mg/m² on day 1, i.v. LV 100 mg/m² followed by i.v. bolus 5-FU 400 mg/m² and 600 mg/m² 22-h continuous infusion on days 1 and 2 every 2 weeks for a maximum of 24 weeks [60]. Cetuximab alone was then permitted in patients with a CR, PR, or SD. All 38 patients were assessed for safety and survival, and 34 patients were assessed for response. The ORR was 44% (95% CI 27.3% to 60.9%) with a CR in four patients (12%) and a PR in 11 patients (32%). Sixteen patients had SD. Median expected OS was 16 months. Grade 3/4 adverse events included neutropenia in 16 patients (42%), acne-like rash in eight patients (21%), diarrhea in three patients (8%), asthenia in two patients (5%), stomatitis in two patients (5%), and hypertransaminasemia in two patients (5%). No cetuximab-related hypersensitivity reaction was reported. There was one (3%) treatment-related death. The combination of PELUF with cetuximab, which is currently being investigated, may achieve similar efficacy results with improved tolerability.

### discussion

Although recent advances in the development of new chemotherapeutic regimens have improved treatment and patient outcomes, advanced gastric cancer still has a poor prognosis. As well as improving response rates and OS, a chemotherapeutic agent should offer improved tolerability and QoL. UFT oral therapy has been shown to have comparable pharmacokinetics to continuous infusion 5-FU with similar efficacy and improved tolerability in the treatment of mCRC [40, 44, 45]. Oral treatment with UFT has also been shown to be preferred by patients to i.v. 5-FU in the treatment of mCRC and to improve QoL [40, 42, 43]. In addition, oral therapy with UFT is more convenient for patients than i.v. 5-FU. UFT therefore represents a logical replacement for 5-FU in chemotherapy regimens for the treatment of advanced gastric cancer.

In advanced gastric cancer, UFT monotherapy is an effective and well-tolerated treatment option with response rates of 16%–29%, OS of 5.8 months, and a low incidence of grade 3/4 adverse events demonstrated in two phase II trials [46, 47]. UFT monotherapy can be particularly useful in elderly or frail patients who are unwilling or unable to tolerate combination therapy. UFT-based combinations are effective and generally well tolerated, with response rates of 35%–57% and OS of 8–15 months [46, 49–51, 53–58]. The efficacy of UFT-based combinations is comparable with that for other combinations, such as irinotecan- and capetibatne-based regimens, with reported ORRs of 20%–58% and 35%–59%, respectively, and median OS of 7–12 months and 9.6 months, respectively [61].

Three-drug combination regimens have been shown to achieve better survival results than two-drug combinations [11]. ECF is one of the most effective three-drug combination regimens available, with ORRs of 42%–46% and median OS of 8.7–9.4 months, and has been considered as standard therapy for advanced gastric cancer [14, 15, 20, 52]. The three-drug combination of UFT with LV and epirubicin and cisplatin (PELUF) is an effective alternative to the ECF regimen with comparable efficacy, as shown by ORRs of 38%–57% and OS of 9.5–15 months, and improved tolerability [53–56]. In one ECF study, 15% of patients experienced complications due to the central venous line while another 16% of patients experienced exit-site infections and 7% had thrombosis [14, 15]. Compared with 5-FU-based combination regimens, UFT-based combinations have the additional advantage of a good tolerability profile, in particular, a low incidence of myelosuppression, mucositis, and HFS.

In conclusion, UFT-based combinations offer the patient an effective, well-tolerated, and convenient alternative to i.v. bolus and continuous infusion 5-FU regimens. The evidence from
published studies supports the role of UFT as a replacement for i.v. 5-FU in the treatment of advanced gastric cancer.

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