Successful Remission of Extensive Liver Metastases in a Breast Cancer Patient with Acute Liver Failure Using a Combined Chemotherapy Regimen with Mitomycin, Folinate, and 5-Fluorouracil (Mi/Fo/FU)

Natalija Stoiber\textsuperscript{a,b}, Nik Hauser\textsuperscript{a} Bernhard Stoiber\textsuperscript{c,b}, Michael K. Hohl\textsuperscript{a} Christof Sohn\textsuperscript{b} Michael H.R. Eichbaum\textsuperscript{b}

\textsuperscript{a}Frauenklinik, Kantonsspital Baden, Schweiz; \textsuperscript{b}Universitätsfrauenklinik Heidelberg, Deutschland \textsuperscript{c}Departement Frauenheilkunde, Universitätsspital Zürich, Schweiz

\textbf{Key Words}
Mi/Fo/FU · Breast cancer · Liver failure · Jaundice

\textbf{Summary}
Background: Liver failure due to disseminated hepatic secondaries represents a therapeutic dilemma in patients with metastatic breast cancer (MBC). Reduced liver function and non-assessable toxicity are limiting factors in the selection of chemotherapeutic agents. Currently, there is no standard treatment after failure of anthracycline- and taxane-based first-line therapies, although there is a variety of well evaluated drugs such as capecitabine. \textbf{Case Report:} We report on a 45-year-old breast cancer patient with disseminated hepatic metastases. She presented in markedly poor condition, showing substantial ascites and extensive jaundice. Blood chemistry analysis showed increased serum levels of liver enzymes (aspartate aminotransferase 271 U/l, alanine transaminase 101 U/l), bilirubin (7.9 mg/dl), and CA 15-3 (1,459 U/l). We induced a palliative chemotherapy with mitomycin, folinate, and 5-fluorouracil (Mi/Fo/FU). The patient improved impressively after the first cycle of systemic therapy. Liver enzymes stabilized continuously, CA 15-3 returned to normal. The patient was discharged 2 weeks after the treatment start. Chemotherapy was well tolerated under dose escalation, no grade 3/4 toxicity was observed. The progression-free interval was 5 months. \textbf{Conclusions:} A combination therapy with Mi/Fo/FU appears to be a reasonable and tolerable alternative salvage strategy for patients with liver failure due to hepatic breast cancer metastases.

\textbf{Zusammenfassung}
Introduction

Jaundice due to disseminated hepatic metastases often represents a complex therapeutic dilemma in the treatment of patients with metastatic breast cancer (MBC). The associated hepatic dysfunction frequently limits the selection of therapeutic agents due to unpredictable toxicity in the setting of altered hepatic clearance. At the same time, the presence of liver metastases is in itself considered as a poor prognostic factor for patients with MBC. Generally, these patients have been shown to be less responsive to chemotherapy when compared to patients without hepatic involvement. The median survival shows a range of 1–20 months after initial diagnosis of liver metastases [1–3]. The principal aims of palliative treatment in this setting are disease control, relief of symptoms, and improvement or maintenance of quality of life. The two most active classes of cytotoxic agents available for the treatment of breast cancer are anthracyclines and taxanes. Taxanes are primarily eliminated via the bile system and feces. Therefore, the use of taxanes in patients with elevated serum bilirubin or pathologic liver function tests is limited. Anthracyclines are predominantly metabolized by the liver. Impaired liver function delays the excretion and increases the accumulation of the drug in tissue and plasma. For doxorubicin, dose reductions are generally necessary depending on the bilirubin levels. Bilirubin levels higher than 5.0 mg/dl are a contraindication for the use of doxorubicin. After the diagnosis of abnormal liver function, all chemotherapeutic agents commonly used for the treatment of MBC have to be administered with caution. Fatal cholestatic liver failure associated with a gemcitabine therapy in MBC has been reported [4]. In addition, vinorelbine has to be administered carefully as the clearance rate decreases in patients with suppression of liver function [5]. We report on the successful treatment of a jaundiced patient with excessive liver metastases of breast cancer and progressive hepatic failure using a combined chemotherapy with mitomycin, folinate, and 5-fluorouracil (Mi/Fo/FU).

Case Report

A 45-year-old woman with a history of stage II breast cancer presented in poor general condition, with loss of appetite, severe fatigue, massive newly developed ascites, distended abdomen, and extensive jaundice. Symptoms developed rapidly over a period of only 3–4 weeks. Breast cancer had been diagnosed 2 years before and had been clinically classified as cT2 cN1 G3 M0. Histologically, an invasive ductal carcinoma could be immunohistochemically confirmed with negative hormonal receptor status (estrogen receptor score 0, progesterone receptor score 0) and absence of any HER2/neu expression (HER2/neu score 0). The patient underwent primary systemic therapy with 4 cycles of pemetrexed/doxorubicin and 4 cycles of docetaxel with suboptimal response, followed by breast conserving surgery and radiation therapy of the breast and regional lymph nodes. The tumor stage according to the final histopathology was ypT1c ypN1a (1/11) G3 L0 R0 M0.

During the current admission, clinical examination revealed an extensively jaundiced patient with findings as described above, resulting in an ECOG status 3. Abnormal blood chemistry reports included elevated bilirubin of 7.9 mg/dl and excessively elevated liver enzymes (aspartate aminotransferase (AST) 271 U/l, alanine transaminase (ALT) 101 U/l). Abdominal ultrasound demonstrated multiple disseminated hepatic metastases in both liver lobes. An endoscopic cholangiopancreatography was performed but did not show any biliary dilatation. The clinical performance status decreased rapidly, and the patient became somnolent. Ascites was released continuously. In addition, thrombocytopenia complicated the situation, and multiple thrombocyte transfusions had to be administered before starting any further treatment. A combined palliative chemotherapy regimen consisting of Mi/Fo/FU was started at 50% of the standard dose for the first 2 cycles. As the performance status of the patient improved, we escalated the dose up to 100% for the following 3 cycles. Chemotherapy was administered in a 3-week interval. The standard-dose regimen consisted of mitomycin C (8 mg/m2 intravenously (i.v.)), folinic acid (500 mg in total), and 5-fluorouracil (750 mg/m2 i.v.) on day 1 plus folinic acid (500 mg in total) and 5-fluorouracil (750 mg/m2 i.v.) on day 2. After the first cycle of chemotherapy, bilirubin initially increased up to 21 mg/dl and then continuously decreased. Six weeks later, the bilirubin serum levels had normalized (fig. 1). Similar findings were observed for the hepatic enzymes (fig. 2). Furthermore, CA 15–3 serum levels decreased continuously (fig. 3). In parallel, the aspartate and alanine transaminase (AST) and alanine transaminase (ALT) during chemotherapy.

Fig. 1. Course of serum levels of aspartate aminotransferase (AST) and alanine transaminase (ALT) during chemotherapy.

Fig. 2. Course of bilirubin serum levels during chemotherapy.

Fig. 3. Course of CA 15-3 serum levels during chemotherapy.
**Table 1.** Palliative chemotherapy regimens after anthracycline and taxane failure according to the current AGO guidelines; table modified and adjusted with respect to the currently documented experience on patients with reduced liver function.

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Oxford LOE</th>
<th>GR</th>
<th>AGO</th>
<th>Treatment experiences on patients with reduced liver function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capecitabine</td>
<td>2b</td>
<td>B</td>
<td>++</td>
<td>treatment under careful observation</td>
</tr>
<tr>
<td>Peg-liposomal doxorubicin</td>
<td>2b</td>
<td>B</td>
<td>+</td>
<td>treatment under careful observation</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>2b</td>
<td>B</td>
<td>+</td>
<td>treatment under careful observation</td>
</tr>
<tr>
<td>Gemcitabine + vinorelbine</td>
<td>2b</td>
<td>B</td>
<td>+/-</td>
<td>not recommended</td>
</tr>
<tr>
<td>Gemcitabine + cisplatin</td>
<td>3</td>
<td>B</td>
<td>+/-</td>
<td>not recommended</td>
</tr>
<tr>
<td>Gemcitabine + capcitabine</td>
<td>3</td>
<td>c</td>
<td>+/-</td>
<td>not recommended</td>
</tr>
<tr>
<td>Ixabepilone + capecitabine</td>
<td>1b</td>
<td>B</td>
<td>+/-</td>
<td>documented so far</td>
</tr>
</tbody>
</table>

LOE = Level of evidence; GR = grade of recommendation; AGO = Arbeitsgemeinschaft für Gynäkologische Onkologie.

**Discussion**

Systemic treatment of MBC with liver involvement and jaundice often is considered futile due to poor prognosis, limited therapeutic options, and the risk of unpredictable toxicity. Anthracycline- and taxane-containing regimens, established as standard chemotherapy treatment options for the first-line treatment of endocrine-resistant MBC, are metabolized and excreted by the liver and may cause severe side effects in patients with impaired liver function [6]. Doxorubicin is considered to be contraindicated for patients with elevated bilirubin serum levels, and the doses of several other drugs have to be adjusted. On the other hand, liver metastases are considered to be less responsive to chemotherapy [4]. So far, there is no consensus defined for the systemic treatment of MBC after failure of a first-line therapy, although there is a variety of drugs that have been well evaluated such as capecitabine (table 1). For patients with a poor clinical performance status, the administration of chemotherapy has to be discussed carefully, as the benefit can be only marginal. Patients with jaundice are at higher risk for toxicity, and treatment options therefore have to be analyzed in detail. A combination chemotherapy consisting of Mi/Fo/FU has been shown to be active and safe in the treatment of patients with advanced liver metastases secondary to breast cancer and hepatic dysfunction [7]. Eichbaum et al. [8] reported a retrospective analysis of 76 breast cancer patients with predominant liver metastases with a clinical benefit for the combined chemotherapy with Mi/Fo/FU at a rate of 58%; similar data are shown on 44 patients with a clinical benefit of 64% [9]. A benefit of up to 50% and a median overall survival of 12.0 months under the treatment with Mi/Fo/FU in patients with impaired hepatic function were reported by Loibl et al. [7]. In summary, Mi/Fo/FU seems to be a well tolerated regimen. In our case, the Mi/Fo/FU regimen was used as a salvage treatment for a breast cancer patient with hepatic failure. The aims of therapy in the palliative setting, such as relief of symptoms, improvement of quality of life, possible prolongation of survival, and therapy administration in an outpatient setting, could successfully be achieved.

In summary, a combined chemotherapy regimen with Mi/Fo/FU appears to be a reasonable and well tolerated alternative salvage treatment option for patients with liver metastases from breast cancer. The regimen is active and feasible also in patients showing clinical signs of reduced or impaired hepatic function. This strategy may offer an important option for MBC patients with reduced performance status and limited treatment options due to hepatic impairment as a result of liver metastases.

**Conflict of Interest**

No conflict of interest for any of the authors can be stated.