Simultaneous 24 h-Infusion of High-dose 5-Fluorouracil and Sodium-Folinate as Alternative to Capecitabine in Advanced Breast Cancer

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Abstract. *Background/Aim: Prognosis of metastatic breast cancer is poor with a 5-year survival rate of 21%. Even though it is incurable, the majority of patients needs a treatment to ameliorate symptoms and prolong survival. If chemotherapy is indicated, toxicity of multi-drug regimens often out-weighs the possible gain, making single-agent chemotherapy the preferred choice. Although capecitabine is frequently used for the treatment of metastatic breast cancer, it is not a therapeutic option for all patients. Patients and Methods: Since simultaneous application of 5-fluorouracil (5-FU) and sodium folinate is a promising alternative treatment for certain patients, we reviewed the cases of 26 patients treated at our site. Results: Progression-free survival (PFS) was 8.6 months and overall survival (OS) was 18.5 months with a beneficial toxicity profile. Conclusion: The efficacy of simultaneous high level 5-FU and sodium folinate is comparable to other frequently used single-agent chemotherapies, while the toxicity profile is favorable.*

The incidence of female breast cancer in the European Union is estimated to be 110 cases per 100,000 women per year, making it the most common cancer in women with an annual increase of 1.5% (5). Even though only 6% of breast cancers are metastatic at the time of diagnosis, 30% to 70% of primary non-metastatic patients experience either local relapse or develop metastatic disease within five years of diagnosis (5, 13). Despite numerous advances in breast cancer therapy throughout the past decades, metastatic disease remains incurable and, once the disease is metastatic, the patients' average 5-year survival rate drops to 21% (5).

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In order to improve survival and ameliorate symptoms of metastatic breast cancer (MBC), treatment is necessary for the vast majority of MBC-patients.

Treatment strategies in advanced-stage breast cancer include endocrine therapy, biological therapy, locoregional interventions, antiosteoclastic therapy and systemic chemotherapy. Decisions on treatment have to consider tumor biology, burden of disease, previous therapy and the patient's general performance. As a cure is unlikely to be achieved, treatment should balance a gain of survival, control of disease and symptoms and the quality of life. If systemic chemotherapy seems necessary, toxicity of multi-drug chemotherapies often out-weighs possible improvements on survival, thus making single-agent chemotherapy a preferable choice for the treatment of progressed stage breast cancer.

Efficacy in breast cancer treatment has been demonstrated for various drugs, including taxanes, anthracyclines, fluoropyrimidines and vinca-alkaloids (9). Examples of published progression-free survival (PFS) data and overall survival (OS) rates of single-agent chemotherapies are shown in Table III.

Despite their high efficacy, the use of taxanes and anthracyclines is limited by their substantial long-term toxicity. Being part of standard adjuvant and first-line chemotherapy regimens for MBC treatment, most patients with progressed stage breast cancer previously received systemic taxane and/or anthracycline containing therapies. Thus, cumulative toxic effects, such as neuropathy and cardiotoxicity, further limit therapeutic choices in heavily pre-treated patients. Taking the patient's general condition into account, single-agent chemotherapy utilizing well-tolerated drugs, such as capecitabine or 5-fluorouracil (5-FU), are the therapies-of-choice for many patients.

5-FU and capecitabine are pyrimidine analogs acting as antimetabolite chemotherapeutics. The 5-FU prodrug capecitabine is a non-cytotoxic, orally administered fluoropyrimidine carbamate that underlies various enzymatic transformations *in vivo* before it is finally metabolized to active 5-FU. Because 5-FU needs intravenous (*i.v.*)

Table I. *Details of patients' characteristics prior to start of 5-FU treatment: Number of patients with respective number of previous therapies.*

	None	One	Two	Three	Four
Adjuvant chemotherapy	7 (29.2%)	16 (66.7%)	1 (4.2%)	0 (0%)	0 (0%)
Endocrine adjuvant therapy	12 (54.2%)	10 (41.7%)	1 (4.2%)	0 (0%)	0 (0%)
Antiosteoclastic adjuvant therapy	20 (83.3%)	4 (16.7%)	0 (0%)	0 (0%)	0 (0%)
Chemotherapy for MBC	9 (37.5%)	10 (41.7%)	3 (12.5%)	2 (8.3%)	0 (0%)
Endocrine therapy for MBC	12 (50%)	9 (37.5%)	2 (8.3%)	1 (4.2%)	0 (0%)
Antiosteoclastic therapy for MBC	11 (45.8%)	9 (37.5%)	3 (12.5)	1 (4.2%)	0 (0%)
Chemotherapy adjuvant and MBC	1 (4.2%)	11 (45.8%)	7 (29.2%)	3 (12.5%)	2 (8.3%)

MBC, Metastatic breast cancer.

application, oral administration is considered a major advantage of capecitabine. Since capecitabine has been approved for treatment of advanced-stage breast cancer in 2001, it has replaced 5-FU treatment in many clinical settings. The main dose-limiting adverse events of a capecitabine therapy are diarrhea and hand-foot-syndrome (3, 4, 8, 15, 16, 18). These two toxicities and the patients' preferences for *i.v.* therapy, and a possible non-adherence to oral application, are the main reasons that capecitabine is not suitable for every patient.

5-FU is administered as an *i.v.* infusion either as a bolus injection or continuous infusion. It causes moderate gastrointestinal toxicity as diarrhea, mucositis and nausea. Depending on the schedule of administration, it results in mild-to-moderate myelosuppression. If extravasal infusion occurs, 5-FU has a low potential of inducing tissue necrosis.

As the binding of the 5-FU metabolite dUMP to thymidylate-synthase is enhanced by the concomitant administration of folinic acid, most regimens combine the administration of 5-FU either with calcium folinate (leucovorin) or sodium folinate, leading to increased response rates by up to 30% (12). One critical drawback of folinic acid usage is its limited half-life time. However, the main advantage of sodium folinate usage compared to calcium folinate is the possibility of a simultaneous application of 5-FU and sodium folinate in one infusion; in contrast to calcium folinate and 5-FU, the mixture of sodium folinate and 5-FU does not result in precipitation of insoluble carbonates. This offers an elegant way of continuous and simultaneous administration of 5-FU and sodium folinate and, thus, a constant biomodulation of 5-FU efficacy for a 24 h application.

Long-term infusion of high-dose of 5-FU/folinate is originally known from some regimens for colon cancer (1) and has also shown high efficacy and a beneficial toxicity profile in MBC (11). Data on direct comparison of high-dose 5-FU and capecitabine in MBC are lacking but a study in metastatic colorectal cancer showed a superior efficacy and less toxicity of long term, high-dose 5-FU/folinate compared to oral capecitabine (14).

Table II. *Details of patients' characteristics prior to start of 5-FU treatment: Number of patients with previous taxane and/or anthracyclin therapy.*

	Yes	No
Adjuvant taxane therapy	12 (50.0%)	12 (50.0%)
Adjuvant anthracycline therapy	14 (58.3%)	10 (41.7%)
Taxane therapy for MBC	11 (45.8%)	13 (54.2%)
Anthracylin therapy for MBC	5 (20.8%)	19 (79.2%)
Taxane therapy adjuvant or MBC	20 (83.3%)	4 (16.7%)
Anthracycin therapy adjuvant or MBC	19 (79.2%)	5 (20.8%)
Taxane and anthracycline treatment adjuvant or MBC	17 (70.8%)	7 (29.2%)

MBC, Metastatic breast cancer.

Based on these experiences, we have been offering 24-h infusions of high-dose 5-FU and sodium folinate at our site, if fluoropyrimidine treatment is required; however, use of capecitabine seems unfavorable for the individual patient due to toxicities or non-adherence of the oral application.

Patients and Methods

We reviewed the cases of 26 patients treated between April 2008 and April 2013 at the Department of Gynecology and Obstetrics, Helios Klinikum Krefeld, Germany. The patients received 2,000 mg/m^2 of 5-FU and 500 mg/m^2 of sodium folinate as a continuous *i.v.* infusion over 24h once weekly for six weeks, followed by a pause of two weeks (1 cycle). Infusion was administered through an implantable port system, using a mechanical pump. Prior to the start of infusion, patients received 1.5mg granisetron *i.v.*. Therapy was administered on an outpatient base.

All decisions concerning treatment were made by a tumor board review. Patients concurrently treated with other cytotoxic agents were excluded from analysis, while simultaneous anti-HER2 and antiosteoclastic treatments were accepted.

Results

Of the 26 reviewed cases, one was excluded due to concurrent use of mitomycin C. A second patient was

Table III. *Baseline demographic and PFS and OS data of own study and published studies of single agent chemotherapeutic agents for MBC.*

	5-FU/sodium folinate	Docetaxel	Paclitaxel	nab-Paclitaxel	PLD	Vinorelbin	Eribulin	Capecitabine
Reference	own data	(12)	(12)	(11)	(17)	(22)	(8)	(15)
Dose (mg/m^2)	2000/500	100	175	300	50	30	1.4	1250
Schedule	d1, 8, 15, 21, 29, 36 q8w	q3w	q3w	q3w	q4w	q1w	d1, 8 q3w	d1-14 bid q3w
Age (median)	58.5 years	56 years	54 years	48.2 years[a]	59 years	72 years	55 years	52 years
ER positive	75%	51.1%	42.0%	NR	35.4%	57%	64%[b]	51.7%
PR positive	75%	36.4%	35.3%	NR	NR	NR	64%[b]	41.7%
Her2 positive	16,7%	NR	NR	NR	NR	NR	16%	20.4%
Visceral metastases[c]	70.8%	NR	NR	29%[d] 29%[e]	58.6%	57%	39%[d]	80.0% 58%[e]
Bone metastases[c]	79.2%	NR	NR	17%	9.4%	25%	60%	NR
Only bone metastases	12.5%	NR	NR	NR	9.4%	NR	NR	NR
CNS metastases[c]	20.8%	NR	NR	NR	NR	NR	NR	NR
Other metastases[c,f]	29.2%	NR	NR	14%	31.8%	18%	NR	NR
Previous CTX for MBC	62.5%	58.2%	52.7%	38%	5%[g]	27%	100%	83.9%
PFS (median)	8.6 months	5.7 months	3.6 months	6.1 months (26.6 weeks)[h]	6.9 months	6 months	3.7 months	4.2 months
OS (median)	18.5 months	15.4 months	12.7 months	14.7 months (63.6 weeks)[h]	21 months	NR	4.2 months	14.5 months

a=Mean age, b=reported as "either estrogen or progesterone positive", c=patients may have metastases at more than one site, d=lung metastases only e=liver metastases only f=cutaneous and/or lymphatic node metastases, g=patients received chemotherapy and/or endocrine treatment for MBC, h=PFS reported in weeks, NR=not reported, PFS=progression-free survival, OS=overall survival, PLD, pegylated liposomal doxorubicin; MBC, metastatic breast cancer; CTX, chemotherapy; CNS, central nervous system.

excluded due to concurrent use of vinorelbine. Twenty-four cases were considered suitable for analysis.

The median age at the beginning of therapy was 58.5 years. The detailed analyses of patients' characteristics and pretreatments are shown in Tables I and II.

The median number of administered therapy cycles of 5-FU was 3.0 and the median duration of treatment was 4.3 months. The median progression-free survival (PFS) was 8.6 months. The median overall survival (OS) was 18.5 months. Therapy was well-tolerated: Of 81 therapy-cycles only 2 (2.5%) resulted in hematotoxicity grade III-IV and 3 (3.7%) lead to grade III-IV elevation of liver enzymes according to NCI common toxicity criteria of adverse events V4.0 (CTCAE). No patient discontinued therapy due to other side effects. Dose reduction was necessary in 8.3% of patients or 2.5% of administered therapy cycles. Statistical data on other toxicities were not obtainable as the recorded data of adverse events lacked accountable graduation defined by CTCAE.

Discussion

The results reported herein show a high effectiveness of a high-dose, long-term infusion of 5-FU and sodium folinate in metastatic breast cancer with a beneficial toxicity profile. Median PFS and OS observed in this study are within the same range as the PFS and OS published from studies with various other single-agent chemotherapeutic agents, which are shown in Table III.

Patients' characteristics, site of metastases, number of previous treatments and biological features of the tumor have a great influence on the course of the disease. Therefore, comparing the results of different studies in the metastatic setting is difficult, as study characteristics, baseline demographics and modalities of study conduction are widely different. Furthermore, due to ethical reasons, there is a lack on reliable data on the course of disease in patients receiving no treatment for progressive MBC.

Baseline demographics of this study differ from those published for other single-agent chemotherapeutics commonly used for MBC (Table III). Many characteristics like age, expression of estrogen, progesterone and HER2 receptors, site of metastases and number of previous therapies are known as independent factors of general prognosis and response to treatment (6, 10). Thus, comparative statistical analysis of the study results does not seem reasonable.

Compared to studies of other frequently used single-agent chemotherapeutics, the baseline patient characteristics show relevant differences: while the median age of 58.5 years and a frequency of HER2-positivity of 16.7% are close to average, the percentage of patients who previously received chemotherapies for MBC is above average. The frequency of

estrogen and progesterone receptor expression and the percentage of patients with visceral and bone metastases are the highest among the selected data (Table III). In conclusion, the majority of patients had a poor prognosis and were massively pretreated.

The expected response to further chemotherapies depends on the extent of previous cytotoxic therapies. Treatment is usually changed if either progression, indicating resistance to the specific treatment, or unacceptable toxicity occurs. Hence, the number of previous antineoplastic therapies might be read as a surrogate for the degree of resistance of the tumor.

Since exposure to the same therapy is not reasonable, the number of adequate treatment choices is reduced with every subsequent line of therapy. As the most efficient agents are usually applied first, it is generally accepted that the probability of response to a newly-commenced therapy decreases with every subsequent line of therapy.

Results of anti-neoplastic treatment for MBC will, therefore, always be more favorable if patients received fewer prior treatments. The fraction of our patients who received previous treatments is in the upper range of the selected studies. This might influence the results obtained in this study, which could lead to shortening rather than prolonging both PFS and OS.

Although the percentage of patients who received prior chemotherapy lies in the upper range (Table III), 37.5% of our patients received 5-FU as a first-line chemotherapy for MBC. Nevertheless, the recommendation for a first-line, single-agent chemotherapy for MBC will usually be either taxanes or anthracylines. As these drugs are part of modern adjuvant regimens, many patients have already received taxanes and/or anthracyclines. Among the patients of this study, 50% of patients were previously treated with taxanes and 58.3% with anthracyclines as adjuvant therapy. A non-negligible number of patients (40.8%) previously received taxanes and 20.8% anthracyclines for MBC. Moreover, 83.3% of the patients were previously treated with taxanes and 79.2% received anthracyclines either during adjuvant treatment or in the metastatic setting. A high percentage (70.8%) even received taxanes and anthracyclines either during adjuvant treatment or for MBC (Table II). Only 4.2% received cytotoxic chemotherapy neither for adjuvant nor for MBC treatment (Table I).

The reasons for treating patients with high-dose 5-FU/sodium folinate as a first-line therapy for MBC were severe toxicities after adjuvant treatment with taxanes and/or anthracyclines or seriously impaired general conditions, which made the re-application of theses drug classes highly questionable.

The site of metastases is known to be one of the strongest predictors of survival in metastatic breast cancer. While patients with solitary bone metastases have a relatively good prognosis, liver or brain metastases are predictors for poor survival. Largillier *et al*. described a median survival of 33.2 months for sole bone metastases, whereas median survival with liver metastases was 12.0 months and 3.0 months with brain metastases, respectively (10).

Compared to the other selected studies in Table III, our patients had the second highest frequency of visceral metastases, predicting a poor survival. Although sole bone metastases are predictors of prolonged survival in general, bone metastases concomitant to other predominant metastases like lung, liver or brain metastases, have to be judged differently; contributing to the overall tumor burden they are more likely to shorten survival than prolonging it.

In conclusion, it is likely that the distribution of metastases among our patients would lead to a shorter rather than a prolonged survival.

As shown in Table III, the frequency of estrogen- and progesterone-positive tumors in this study is the highest among the selected studies. While, in general, expression of estrogen and progesterone receptors is considered to be a predictor of prolonged survival in breast cancer (10), the implications in progressive MBC are discussed controversially (2). Some studies suggest a better response of estrogen-positive MBC to chemotherapy, while other studies show less response compared to estrogen-negative disease. A commonly proposed explanation for these contradictive results is the difference in pre-treatment of patients with estrogen-positive and -negative disease: While patients with estrogen-positive tumors will receive endocrine treatment first, and therapy is switched to chemotherapy upon progression, patients with estrogen-negative disease will receive chemotherapy upon diagnosis. Altogether, it is unclear how the different proportions of estrogen- and progesterone-positive patients influence the results of the studies.

Despite these limitations, with an observed PFS of 8.6 months and OS of 18.5 months, the efficacy of long-term, high-dose 5-FU/sodium folinate is favorable compared to the results of other single-agent chemotherapies (Table III). Nonetheless, prospective, controlled trials are needed to confirm these findings.

Regarding the toxicity profile, the data obtained from the patients' files are limited. While hematotoxicity and liver toxicity was well-documented, the documentation of other toxicities lacked a finer graduation. Thus, the statistical analysis of other toxicities was not rational. However, estimating the extent of other toxicities is still possible: dose reduction was necessary in 2.5% of administered therapy cycles, indicating a low incidence of severe adverse events. In addition, no patient discontinued treatment due to unacceptable side-effects. Although statistical evidence is not obtainable, these findings indicate a favorable toxicity profile of simultaneous high-level 5-FU/sodium folinate, if

compared to the toxicities reported for other frequently used single-agent chemotherapies like capecitabine. The favorable toxicity profile of high-dose 5-FU/folinate in breast cancer was already substantiated by other clinical data (17).

Although results from clinical trials show a favorable toxicity profile for capecitabine, patients in daily routine experience significant toxicities. Most frequent side-effects are hand-food-syndrome (HFS) and toxicities that affect the gastrointestinal tract. In pretreated patients with MBC, the published rates of common side effects, such as diarrhea (CTC grade III-IV), range between 8 to 30%, for HFS (CTC grade III-IV) between 9 to 42% and for nausea (CTC grade III-IV) between 6 to 27% (3, 4, 8, 15, 16, 18), requiring dose reductions in up to 50% of patients (3, 15).

Leaving aside the potential side-effects, in our clinical practice we feel that oral intake of capecitabine may not be suitable for every patient. This statement is confirmed by findings from studies concerning a variety of cancer entities, *e.g.* colorectal or ovarian cancer (1, 7). If the patients can choose between oral and intravenous therapy, the majority selects the *i.v.* application route (7). Simultaneous managing of the capecitabine intake schedule, supportive drug intake and dealing with potential side effects requires the patient's full attention. This might, for some patients, result in a mental overload and a reduced adherence, especially if comorbidities require further drugs to take. Additionally, for an average adult, the single-dose of 1,250 mg/m^2 capecitabine is contained in 5-6 tablets, thus the twice-daily oral intake does not necessarily seem too convenient.

In conclusion, we may point out that the median PFS and OS observed in this study are similar to data reported for other chemotherapeutics (Table III). These findings suggest that the efficacy of weekly 24-h high-dose 5-FU/sodium folinate is not inferior to other single-drug chemotherapies. Assessed toxicity to bone marrow and liver function is very low and the low rate of dose reduction and discontinuation of treatment, due to side effects, suggest a favorable tolerability of the treatment. Prospective, controlled trials are needed to confirm these findings. 5-FU/sodium folinate may comprise a reasonable therapeutic option in selected patients, especially if clinical or personal reasons lead to non-adherence of an oral therapy.

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