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Ifosfamide/etoposide and mesna uroprotection in advanced breast cancer*

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Summary. The object of the study was to evaluate the effectiveness of ifosfamide/etoposide and mesna therapy in advanced breast cancer. A total of 44 patients with breast cancer were included in the trial. Eligibility criteria included measurable, refractory disease; prior anthracycline therapy (or its contraindication); a life expectancy of at least 3 months; and adequate hepatic, renal, CNS and bone marrow function. All patients were ≤ 70 years of age and had a Karnofsky performance status of $\geq 50\%$. There were 36 evaluable cases. Sites of metastatic disease included bone (19), skin (18), liver (9), lung (14), lymph node (19), and miscellaneous (7). Treatment consisted of 1,500 mg/m^2 ifosfamide given i.v. on days 1–5, 120 mg/m^2 etoposide given i.v. on days 1–3, and 400 mg i.v. mesna given with and at 4 and 8 h after ifosfamide. Cycles were repeated every 28 days. Initial doses were reduced by 25% or 50% in patients who had previously undergone both chemotherapy and radiotherapy. A median of 4 cycles (range, 2–8) were given. The myelotoxicity was marked: WHO grades 3/4 leukopenia ($n = 37$), grades 3/4 thrombocytopenia ($n = 12$), and grades 2/3 anemia ($n = 13$). Due to myelotoxicity, dose reduction or prolongation of treatment-free intervals was necessary in 28 cases. Alopecia was seen in 35 patients and CNS toxicity, in 8. Partial remission (PR) was obtained in five cases and complete remission (CR), in three. Sites of response included the lung (5), skin (4), lymph node (5), and peritoneum (1). The duration of response was 4 ($n = 2$) and 8 ($n = 1$) months for CR and 2 ($n = 2$), 6 ($n = 2$), and 10 ($n = 1$) months for PR. We conclude that the ifosfamide/etoposide and mesna regimen is effective, but its myelotoxicity is treatment-limiting.

Introduction

For patients with advanced breast cancer, the expected results from cytotoxic treatment continue to be most unsatisfactory. Under the most commonly accepted therapeutic regimens, only approximately 50% of patients show an objective response, and most of these responses are partial [24]. It is therefore of utmost importance that new substances or non-cross-resistant chemotherapeutic combinations be developed to improve treatment results.

Ifosfamide has long been recognized as one of the most effective substances available to medical oncologists [5, 11, 13, 20, 25, 27, 28]. More than a decade ago it was shown that with single-agent ifosfamide, a first-line response rate of well above 30% could be obtained in advanced breast cancer [1, 6, 15, 20]. Unfortunately, because of the drug's severe urotoxicity, it was concluded at that time that ifosfamide should not be further considered as an alternative in the treatment of advanced breast cancer [8].

With the development of the sulfhydryl compound mesna, however, an effective uroprotective agent has now become available, which has justified a reconsideration of ifosfamide's use in clinical trials. In the case of advanced breast cancer, mesna's uroprotective qualities have also led to an intensification of clinical studies evaluating ifosfamide and its use in combination chemotherapy [2, 16]. The rational behind these studies is that ifosfamide has proved to be more effective than cyclophosphamide [17] while tending to be less myelosuppressive [3], which would suggest that ifosfamide could well be a more ideal component of combination chemotherapy [12].

In our search for a new, non-cross-resistant combination chemotherapy for advanced breast cancer, we decided to initiate a phase II study combining ifosfamide, mesna, and etoposide. Despite the fact that the effectiveness of etoposide as a single agent in breast cancer treatment has as yet failed to be conclusively established in a phase II study [10, 26], this combination nonetheless appeared to be promising, because the individual components have produced successful results in the treatment of other solid tumors and hematological neoplasms [7, 9, 11, 14].

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Table 1. Patients' characteristics ($n = 44$)

Age:	Median	56 years
	Range	31–70 years
Karnofsky performance status	≥ 80%	16
	50%–70%	28
Menopausal status:	Premenopausal	16
	Postmenopausal	28
Steroid receptor status:		
ER (fmol/mg)	Positive >10	6
	Negative <10	15
	Unknown	23
PR (fmol/mg)	Positive >20	6
	Negative <20	15
	Unknown	23

ER, estrogen receptor; PR, progesterone receptor

Table 2. Pretreatment

Chemotherapy	Adjuvant (*n*)	Palliative first-line (*n*)	Second-line (or more) (*n*)
CMF	4	4	19
VAC	–	19	4
AC	9	5	1
Miscellaneous	5	10	8
Total	18	38	32
Radiotherapy:	Adjuvant (*n*)	Palliative (*n*)	
	23	11	

Table 3. Sites of metastatic disease

Site	Incidence (*n*)	*Sites/patient*	*Incidence (n)*
Lung	15	1	16
Liver	11	2	15
Bone	25	3	8
Lymph nodes	23	4	5
Skin	13		
Miscellaneous	3		

Table 4. Correlation of tumor response to ifosfamide/mesna/etoposide and cytotoxic pretreatment

Quality	Response duration (months)	Site	Pretreatment: type of therapy
1. CR	4	Skin, lymph node	FAC (5), M-vinblastine (18)
2. CR	4	Lung	AC (6), CMF (5), Mit-C (6)
3. CR	8	Peritoneum	AC (5)
4. PR	2	Skin, lymph node	VAC (6), CMF (5)
5. PR	10	Lung, lymph node	VAC (6), CMF (4)
6. PR	2	Lung, Skin, lymph node	AC (3), CMF (8)
7. PR	6+	Lung, lymph node	CMF (8), Noste (2)
8. PR	6	Lung, skin	EC (6)

Numbers in parentheses represent the number of courses received
A, Adriamycin; C, cyclophosphamide; E, 4-epidoxorubicin; M, methotrexate; Mit-C, mitomycin C; F, 5-fluorouracil; V, vincristine; Noste, novantrone-sterecyt

Patients and methods

Patients. A total of 44 patients were included in this clinical study. Eligibility criteria included histologically proven, bidimensionally measurable, refractory disease; prior anthracycline therapy (or its contraindication); a life expectancy of at least 3 months; and adequate hepatic, renal, CNS, and bone marrow function. All patients were ≤ 70 years of age and had a Karnofsky performance status of ≥ 50%. Details concerning age, Karnofsky status, menopausal status, steroid receptor status, pretreatment (chemotherapy and radiotherapy), as well as incidence and sites of metastatic disease for the patients included in the study can be found in Tables 1–3.

Treatment. The treatment schedule consisted of 1,500 mg/m^2 i.v. ifosfamide given as a 1-h infusion on days 1–5; 120 mg/m^2 i.v. etoposide given as a 1-h infusion on days 1–3; and 400 mg mesna given as an i.v. bolus with and at 4 and 8 h after ifosfamide on days 1–5. The treatment cycle was repeated every 4 weeks. In accordance with the suggestions of Rodriguez et al. [22], initial ifosfamide doses were reduced to 75% in 11 patients (25%) and to 50% in 9 cases (20%) because of intensive pretreatment.

Evaluation. Responses were evaluated according to International Union Against Cancer (UICC) criteria [18]. A complete response (CR) was defined as the disappearance of all measurable lesions for at least 2 months, and a partial response (PR) was defined as a reduction in tumor size of >50% and the absence of new lesions for at least 2 months. Effusions and bone lesions were not regarded as being objectively measurable. No change (NC) was defind as either stabilization or a reduction in tumor parameters of <50% without progression of other lesions for at least 3 months. Progression of disease (PD) was defined as an increase of >25% in any of the metastatic lesions based on the maximal response observed. Duration of response was calculated from the start of treatment until disease progression. Toxicity was evaluated according to WHO criteria. For each patient, the highest grade of toxicity that occurred is cited.

Results

A total of 135 treatment cycles were given. Of the 44 patients treated, 36 received at least 2 therapy cycles (median, 4; range, 2–8) and were thus eligible for inclusion in the evaluation of response. Of the 36 patients, 8 (22%) responded; a PR was obtained in 5 and a CR, in 3 patients. Eight patients achieved stabilization of disease and clinical improvement. In all, 20 patients showed PD after the completion of 2 treatment cycles. Sites of response included the lung (5), skin (4), lymph node (5), and peritoneum (1). The correlation of cytotoxic pretreatment to response is shown in Table 4. Interestingly, all responders had undergone cyclophosphamide pretreatment. The median duration of response was 4 months (range, 2–10 months) for objective responders (CR+PR).

Myelotoxicity was marked, with WHO grades 3/4 leukopenia ($n = 37$) and grades 3/4 thrombocytopenia ($n = 12$). Because of myelotoxicity, dose reduction or prolongation of treatment-free intervals was necessary in 28 patients. However, treatment-related infections were relatively rare, achieving a severity of grade 3 in only three cases. Alopecia of grades 2/3 developed as expected in the majority of patients ($n = 35$). CNS toxicity was not a significant clinical problem.

Discussion

Ifosfamide is known to be effective in the treatment of metastatic breast cancer. As long as a decade ago, the objective remission rates were quoted as lying well above 30% [1, 6, 15, 20]. However, further clinical trials based on these positive results could not justifiably be undertaken due to the severe urological side effects associated with the use of ifosfamide. Because of the uroprotection offered by the sulfhydryl compound mesna, such toxic side effects can now largely be avoided. As a result, a number of new clinical studies focusing on ifosfamide have recently been initiated, many of which concern its use in combating breast cancer. Preliminary results evaluating the effectiveness of ifosfamide with mesna uroprotection as both single-agent as well as combination therapy appear to be promising in pretreated, advanced breast cancer [2, 16, 28]. These initial results mainly concern the use of ifosfamide plus mesna in combination with methotrexate and 5-fluorouracil (5-FU), since experimental tumor systems and previous clinical studies suggested that ifosfamide, because it is more effective and would appear to be less myelotoxic than cyclophosphamide, could successfully be substituted for the latter as a more ideal component in the generally accepted CMF (cyclophosphamide, methotrexate, and 5-FU) regimen [3, 17, 22]. The total ifosfamide dose per treatment cycle varied in these studies from 2,500 to 6,000 mg/m^2. The objective remission rates were reported to lie between 12% and 25%; however, it should be borne in mind that the total number of patients who clinically benefitted from the treatment was actually much higher, since there were many who showed no change.

Our results with ifosfamide plus mesna and etoposide essentially confirm the above findings, since they lie within the range that can be realistically expected for intensively pretreated patients [4, 28]. Eight (22%) of the women showed an objective response; three of them responded completely and five, partially. Another eight women reacted with stabilization of disease. Unfortunately, the number of CRs did not lead to an improvement in the median duration of response achieved in comparable studies. This all too common finding again demonstrates the limited significance of the term "quality of response" in clinical studies dealing with cases of advanced cancer, as was recently pointed out by Becher et al. [2]. On the positive side, it should be noted that all of the women who responded to our ifosfamide regimen were intensively pretreated with anthracyclines and with cyclophosphamide. Our study would thus confirm what previous experimental studies and clinical trials involving other neoplasms have suggested, namely, that ifosfamide is more effective than cyclophosphamide and that it can be successfully given even following intensive pretreatment with the latter. The metastases that most often responded to our treatment were those affecting the skin, lung, peritoneum, and lymph nodes. These results are similar to those reported for ifosfamide/methotrexate/5-FU (IMF) therapy [2]. Our treatment appeared to be less effective for liver metastases.

In terms of toxicity, our patients repeatedly reported that ifosfamide/mesna/etoposide treatment was relatively easy to tolerate; it should be remembered that these pretreated patients had much experience with cytotoxic drugs on which to base their opinions. Not only did we find no evidence of serious ifosfamide/mesna-associated CNS toxicity as reported in detail by Meanwell et al. [21], but even the gastrointestinal side effects were minimal to moderate, and this was especially appreciated by the patients. The main cause for concern in our regimen proved to be myelotoxicity, which often reached WHO grades 3 and 4 and in several instances led to prolonged hospitalization of the patients involved. However, there were no occurrences of severe septic events. In attempting to evaluate the possible cause of the hematological toxicity experienced by our patients, the first consideration should perhaps be given to the patients' history of intensive radiotherapeutic and cytotoxic pretreatment. On the other hand, with an ifosfamide dose per cycle totalling 6,000 mg/m^2, it may well be that a borderline tolerance level is reached which, when combined with a second myelotoxic substance, cannot be overlooked as a possible source of toxicity in the case of intensely pretreated patients. Such reactions can apparently occur, even when the dose adjustment recommendations arising from the experiences described by Rodriguez et al. [23] are closely followed.

Nonetheless, we would conclude that ifosfamide/mesna/etoposide is a non-cross-resistant combination that can be given as a means of palliation in advanced breast cancer patients who have been pretreated with anthracyclines and CMF. At the same time, it should be pointed out that this recommended combination chemotherapy is currently competing with a higher-dose ifosfamide monotherapy from which a comparable number of patients has been reported to benefit [28]. In our opinion, the first priority of future clinical studies to achieve improvement in the first-line therapy of metastatic breast cancer patients should be given to various combinations of ifosfamide/mesna, methotrexate, and 5-FU. On the basis of our experience with ifosfamide plus mesna and etoposide, it would appear that this combination is less advantageous than IMF, not only because of the uncertain effectiveness of etoposide against breast cancer [10, 19, 26], but also because of the possible cumulative effect of ifosfamide and etoposide on myelotoxicity.

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