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NAŠE PRVNÍ VÝSLEDKY LÉČBY METASTATICKÉHO KARCINOMU PRSU IFOSFAMIDEM A PACLITAXELEM PŘI RECIDIVĚ PO ANTRACYCLINU

IFOSFAMIDE AND PACLITAXEL TREATMENT IN METASTATIC BREAST CANCER, RELAPSED AFTER ANTRACYCLINE TREATMENT: OUR FIRST RESULTS

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Souhrn: Kombinační chemoterapie má při léčbě karcinomu prsu důležitou úlohu. Jako podpůrné prostředí může její aplikace prodloužit celkové přežití bez obtíží. Ifosfamid a Paclitaxel mají schopnost vyvolat při tomto onemocnění účelovou reakci nádoru. Jejich kombinace je novým časovým plánem při ošetřování pokročilého karcinomu prsu. 13 pacientů, u nichž došlo po antracyclinu k recidivě, dostávalo tuto kombinaci buď jako výchozí podpůrnou terapii nebo jako chemoterapii první linie. Léčba 1. den sestávala ze 135 mg/m^2 paclitaxelu a pokračovala 2.–4. den 1 700 mg/m^2 ifosfamidu. Pacienti kombinaci velmi dobře snášeli. Výsledkem je jedna celková a pět částečných reakcí. Zásluhou jejich různých mechanismů činnosti a jednoznačně nehematologických profilů toxicity bude pravděpodobně kombinace ifosfamidu a paclitaxelu lákavou alternativou při ošetřování metastatického karcinomu prsu.

Summary: Combination chemotherapy plays an important role in the treatment of breast cancer. Administration of them like adjuvant setting can prolong the disease free and overall survival. Both ifosfamide and paclitaxel are able to produce objective tumor response in this disease. The combination of them is a new schedule in the management of advanced breast cancer. 13 patients relapsed after antracyclin based adjuvant or first line chemotherapy recieved this combination. Treatment consisted of 135 mg/m^2 paclitaxel on day 1, followed by 1700 mg/m2 ifosfamide on days 2-4. The combination was well tolerated. One complete and five partial responses resulted. Due to their different mechanisms of action and their distinct non-hematological toxicity profiles, the combination of ifosfamide and paclitaxel seems to be an attractive option in the management of metastatic breast cancer.

Introduction

Cytotoxic medication plays a central role in the treatment of breast cancer. Adjuvant therapy can reduce the risk of recurrence and death among women with early –stage disease.[1] In advanced stage breast cancer chemotherapy offers a significant opportunity for palliation and longer survival.[2] Until the 1990's the classical chemotherapy of breast cancer has been based on several families of drugs ranging from alkylators to intercalators, antimetabolites and tubulin inhibitors.[3] Although many cytotoxic drugs have proven activity in breast cancer, from the 1980's combination of alkylating agents and antracyclines have been being most extensively used as first line treatment of advanced breast cancer.[4,5,6] Antracyclines are among the most active first line drugs in advanced breast cancer, achieving objective response rates of 40-50% when used as single agent[7] and of up to 70% in combination regimen.[8] Inspite of this the overall survival of treated patients did not change singificantly because of the low complete remission rate and short duration of responses.[9] However, increasing use of anthracyclines in adjuvant treatment in premenopausal and postmenopausal patients has led to limitation of their use in relapsed patients.[10,11] Among the novel agents that emerged in the 1990s (ie.taxanes, vinorelbine, gemcitabine) the taxanes appear to be the most promising and probably will be remembered in the future as the chemotherapies of the 1990s.[3] The first taxane is the paclitaxel, with schedule-dependent activity. Used as first line treatment its' response rates ranges from 29% to 62%.[12] In a phase II trial it was found 26% response rate in antracycline-resistant patients and 36% as a first line therapy also in a phase II randomised study.[13] Preclinical studies demonstrate additive and/or synergistic interaction between taxanes and ifosfamide. Ifosfamide is an isomeric analogue of cyclophosphamide. Early preclinical studies demonstrated a wider spectrum of ifosfamide activity compared with it's parent compound. In addition incomplete cross-resistance between the various alkylating agents was observed. Using like first-line therapy, ifosfamide has also reported to produce objective tumor responses in 45% of cases, complete responses has occured in 10% of the patients.[15] In patients treated previously by cytotoxics, ifosfamide treatment can lead to objective responses in 15-20% of cases.[16,17] Based on the above mentioned the combination of ifosfamide and paclitaxel seems to be an attractive option in the management of metastatic breast cancer, like salvage regimen.[18] Due to the different me-chanisms of action of ifosfamide and paclitaxel and their distinct non hematological toxicity profiles, we used this combination to the patients who relapsed after the antracyclin based adjuvant or first line chemotherapy.

Patients and Methods

Treatment program design

This was a treatment program for investigating the effect of ifosfamide and paclitaxel combination treatment after failure of antracyclin treatment in advanced breast cancer. Our plan was to determine the time to progression (TTP), the survival and to measure the tumor response.

Patient population

To enter this treatment program the patients were required to have histologically proven primary breast cancer that had progressed after a complete antracyclin based adjuvant chemotherapy or after first line antracyclin treatment for advanced disease. Prior hormonal therapy for advanced disease was not allowed. Up to now 13 patients were included in the program.

Examination

Blood cell count, serum biochemistry (AST, ALT, alkaline phosphatase, bilirubin, creatinine, calcium, sodium, potassium), ECG and staging investigations: chest X-ray, bone scintigraphy and bone X-ray, when it was indicated, and ultrasound or computer tomography of the liver were performed before the therapy started. Laboratory values: AGC≥1500/uL, platelets ≥100,000/uL, total bilirubin £2x ULN, AST or ALT £2,ULN. ULN= upper limit of normal range

Lesions were assessed every third course, at treatment discontinuation. Response evaluation was performed according to WHO recommendation with modification by the EORTC.9

Treatment program

Patients received paclitaxel as a 3-hour intravenous infusion on day 1 of each cycle in doses of 135mg/m^2. Premedication was given before the administration of paclitaxel: methylprednisolone 100 mg orally, midnight and at 6 o'clok am before paclitaxel, plus chloropyramine 50 mg iv and ranitidine 50 mg iv 30-60 min before, and ondasetron 8 mg iv 30 min before the drug administration. Ifosfamide was given at 1,8g/m^2 with mesna 360mg/m2 iv., 15 min before respective 4 and 8 hours later , on days 2-4. The two drugs were given on separate days because of the long administration period of each.

Table 1. Patient Characteristics N=13

Median age (range)	48 (27—66)
ECOG Performance Status	
0–1	10
2	3
Prior chemotherapy for adjuvant disease: 8	
FEC /FAC	4
4Ag8CMF	4
1st line chemotherapy for metastatic disease	5
Organ involved at time of metastases:	
lung	7
lymph nodes	6
liver	5
bone	4
chest wall	4
pleural effusion	2
Number of organs involved	
=1 5	
=2 6	
≥3 2	

Table 3. Response to paclitaxel and ifosfamide

CR (complete remission):	1
PR (partial remission):	5
SD (stable disease):	3
PD (progressive diasease):	4

Toxicity

The combination of ifosfamide and paclitaxel was well tolerated. Nausea and vomiting WHO grades 1-2, alopecia grade 2 and neutropenia grade 1-2 were seen in most patients. There was no grades 3-4 infection. Grade 3 nail toxicity in 1 patient, grade 3 fluid retention in 1 patient, grade 3 neuropathy in 2 patient were detected. Four patients had reversible grade 3 neutropenia. Less common toxic effect consisted of a mild local phlebitis in 1 patient and a mild cutaneous hypersensitivity reaction also in 1 patient.

Results

13 patients with metastatic breast cancer were treated with combination of ifosfamide and paclitaxel, between December 1997 and July 2000 in four oncological centers. There were given 84 cycles (2-12), median cycles per patients 6,46. The median survival was 21,6 month; the progression free survival 7,0 month. Overall responses (CR+PR) were seen at 6 patients, stable diseases at 3 patients and progression of the process at 4 patients. (table 3.)

Discussion

In the preclinical studies the cell-killing effects of chemically induced DNA damage by alkylating agents are intensified by paclitaxel.[19,20] In the clinical setting paclitaxel has shown enhanced activity and possible synergistic effect when combined with alkylating agents ifosfamide/cyclophosphamide.[21] Paclitaxel inhibits the energy-dependent enzymatic reactions, by disengaging activated intracellular phosphate (e.g.ATP and GTP), required for repair of the DNA damage induced by ifosfamide (prevention of DNA strand preparation and unwinding). The synergistic interaction between paclitaxel and DNA-damaging agents is based on the ability of paclitaxel to slow the DNA-process. For this reason is important the administration of ifosfamide after paclitaxel.[22] The cytotoxic interaction of 4-OOH-ifosfamide with various other clinically relevant drugs, including doxorubicin, cisplatin, and paclitaxel were evaluated by classic isobologram analysis in a panel of established human ovarian and breast cancer cell lines. On the basis of isobologram analyses of drug interactions in vitro was demonstrated that applying ifosfamide before paclitaxel resulted in drug antagonism, administering ifosfamide concurrently with paclitaxel was additive, and administering ifosfamide after paclitaxel was synergistic.[23,24] In the first phase I studies on the combination of ifosfamide and taxanes the major toxicitiy was granulocytopenia grade 3 and 4, wich occurred in 89% of all courses, and appeared to be ifosfamide dose dependent.[25] The optimal doses of paclitaxel (135-200mg/m^2) and ifosfamide (1,5-5,0g/m^2) have to be established in the future.[26]

Conclusions:

Our data should indicate that ifosfamide -and paclitaxel - based combination programs are potential clinical values for metastatic breast cancer relapsed after antracyclin therapy. The regimen is feasible for patients with tolerable toxicity. Further studies with more patients are warranted.

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