Anti-Cancer Drugs 2000, **11,** pp. 269–273

Case report

Intra-arterial mitoxantrone and paclitaxel in a patient with Stewart–Treves syndrome: selection of chemotherapy by an *ex vivo* ATP-based chemosensitivity assay

M Breidenbach,[1] D Rein,[1] T Schmidt,[1] W Heindel,[2] H Kolhagen,[1] P Mallmann[1] and CM Kurbacher[1]

[1]Department of Gynecology and Obstetrics, University of Cologne, 50931 Cologne, Germany. [2]Department of Radiological Diagnostic, University of Münster, 48149 Münster, Germany.

We report on a 72-year-old patient developing Stewart–Treves syndrome (STS) of the right arm 9 years after curative irradiation for ipsilateral stage III breast cancer. Facing the poor track record of both irradiation and chemotherapy in this highly malignant lymphangiosarcoma, amputation was recommended but refused by the patient. Therefore, limb conserving-therapy using three courses of intra-arterial mitoxantrone (MX) and paclitaxel (PTX) was attempted. This novel chemotherapy protocol was selected by pretherapeutic *ex vivo* ATP-based chemosensitivity testing of autologous tumor tissue. The patient experienced complete response, which was subsequent histologically confirmed by compartment resection. When developing recurrent STS outside of the perfused area 6 months after primary therapy, the patient was retested and reinduced with three other courses of intra-arterial MX/PTX which again produced durable complete remission. This case demonstrates the benefit of indivdualized therapy in this prognostically desperate disease allowing both limb conservation and maintained quality of life. [© 2000 Lippincott Williams & Wilkins.]

Key words: ATP tumor chemosensitivity assay, intra-arterial chemotherapy, mitoxantrone, paclitaxel, Stewart–Treves syndrome.

Introduction

Primarily described in 1948, the Stewart–Treves syndrome (STS) is a malignant angioplastic disease induced by chronic lymphedema which often persists for years before malignant transformation occurs.[1] Ninety percent of the lymphedema-associated angiosarcomas develop in the area of the upper limb, most frequently seen after radical surgery and/or radiotherapy performed for primary breast cancer.[2] In fewer cases, STS has been reported after post-traumatic, congenital, parasitic of spontaneous chronic lymphedemas.

The typical clinical performance of STS is a progressive swelling of the involved extremity accompanied by unspecified skin changes. These are followed by purple s.c. nodules, which spread over the extire extremity and give rise to plum-sized, partly ulcerating tumors. The histopathological appearance of this distinct neoplastic entity is characterized by multiple, well-differentiated lymphatic vessels with irregular anastomoses. Additionally, atypical endothelial cells and accumulations of anaplastic tumor cells are seen, partly locking vessel lumina. Animal studies have shown that chronic lymphostasis could induce lymph vessel proliferation with mutations and malignant endothelial transformation.[3] Additionally, chronic lymphostasis can result in a reduced number of local lymph nodes which thus may compromise locoregional immune reactions.

In the last two decades, the radical Rotter–Halsted operation has been substituted by less invasive surgical techniques performed for primary breast cancer which also include more conservative procedures of axillary lymph node dissection. Moreover, most radiotherapists now abstain from routinely irradiating the axilla after lymphadenectomy. This has reduced the incidence of chronic lymphedema which formerly was one of the major sequelae of loco-regional breast cancer treatment from 40 to 4%. Therefore, STS has become a rare complication of primary breast

Correspondence to M Breidenbach, Department of Gynecology and Obstetrics, University of Cologne, Kerpener Strasse 34, 50931 Cologne, Germany.
Tel: (+49) 221 478 4910; Fax: (+49) 221 478 4929;
E-mail: Martina.Breidenbach@medizin.uni-koeln.de

carcinoma therapy. Until today, radical excision or even amputation is considered the therapy of choice for STS.[4] Only small series of patients in which limb conservation by radiotherapy or locoregional chemotherapy was attempted have been published so far—none of them providing satisfying results. Even after complete resection, the prognosis of STS remains poor due to the frequent occurrence of distant metastases. The mean survival time without therapy is only 6 months and may be increased to a maximum of 16–20 months after appropriate surgery.[4,5] Unfortunately, systemic empirical chemotherapy does not display major activity in STS.

This report presents a case of a woman with STS of the right arm occurring 9 years after curative irradiation of a stage III breast carcinoma. In order to prevent her from amputation, the patient was treated with intra-arterial chemotherapy selected by an *ex vivo* ATP-based chemosensitivity assay.

Case report

In 1989, the now 72-year-old female Caucasian patient was diagnosed with locally advanced carcinoma of the right breast with skin ulceration, invasion into the pectoral muscle and bulky metastates involving the ipsilateral axillary lymph nodes. Clinical tumor stage was T4c N2 M0. After diagnosis of invasive ductal carcinoma was confirmed by local biopsy, the right breast, chest wall and locoregional nodes were irradiated with a total dose of 50 Gy. Since radiotherapy produced complete response, no major surgery was performed in this patient.

Immunohistochemically, the tumor was weakly positive for estrogen and negative for progesterone receptors. Therefore, Tamoxifen was given for 5 years at a daily oral dose of 40 mg. Until today, the patient is free from recurrent breast carcinoma.

In May 1997, the patient developed acute grade 3 lymphedema of her right arm accompanied by rapidly growing livid nodules that expanded to plum-sized tumors. Assuming that these symptoms were caused by inflammatory exanthema, the patient received both local anti-inflammatory treatment as well as oral clindamycin given for 10 days. Due to persistent symptoms, the patient underwent skin biopsy. The histology of the tumors revealed a nodular accumulation of atypical cells. The neoplastic tissue partly showed signs of vessel-like structures containing erythrocytes. Another portion presented with lymph vessel-like structures. Mitotic activity could be found within the whole specimen, so that the diagnosis of STS was made. Exarticulation of the involved extremity was recommended but refused by the patient. However, primary radiotherapy of the lesions was not considered promising. Thus, the patient was referred to our institution to explore the possibility of a limb-conserving approach based on locoregional chemotherapy.

Among a variety of anticancer drugs used for intra-arterial chemotherapy of soft tissue carcomas, doxorubicin (DOX) has been most extensively studied.[9] However, the experience with intra-arterial DOX in STS is limited and results have not always been successful. Since no other established cytostatic regimen exists for STS, the decision was made to take another biopsy for pretherapeutic drug testing using the ATP tumor chemosensitivity assay (ATP-TCA). This assay utilizes a commercially available kit technique (TCA 100; DCS Innovative Diagnostik Systeme, Hamburg, Germany). Detailed ATP-TCA methodology has been described elsewhere.[7] The ATP-TCA compares favorably to previous sensitivity assays in terms of robustness, standardization and reproducibility.[6] Generally, assay results are available after 5–7 days of incubation. Its high efficacy allows testing of four to six different single agents or combinations at six different concentrations using only 10^6 viable tumor cells. Promising *ex vivo/in vivo* correlations have been reported and, most recently, the ATP-TCA has been successfully used to direct chemotherapy of individual patients with both breast and ovarian carcinoma.[6,7]

Due to the relatively small amount of tumor material obtained by cutaneous biopsy, two different regimens were tested in this particular case: DOX which may be regarded as standard, and a combination of mitoxantrone (MX) and paclitaxel (PTX). The latter regimen was chosen because potentiating combination effects of two drugs in both breast and ovarian tumors have previously been demonstrated.[8]

Due to its favorable physico-chemical profile, MX is widely used for locoregional chemotherapy of human cancers.

PTX provides similiar characteristics mainly related to its high molecular weight, and has already been used for both intraperitoneal and intrapleural instillation. Thus, combining both agents was considered a logical next step in order to develop a new active regimen for locoregional application.

Both DOX and MX/PTX were tested at therapeutic and supratherapeutic levels. The results of the chemosensitivity assay are shown in Figure 1(a). A clear dose–response relationship was found for both regimens. Generally, MX/PTX appeared to be more active than DOX which failed to produce total tumor cell kill even at high concentrations. In particular, the novel regimen induced complete tumor cell inhibition

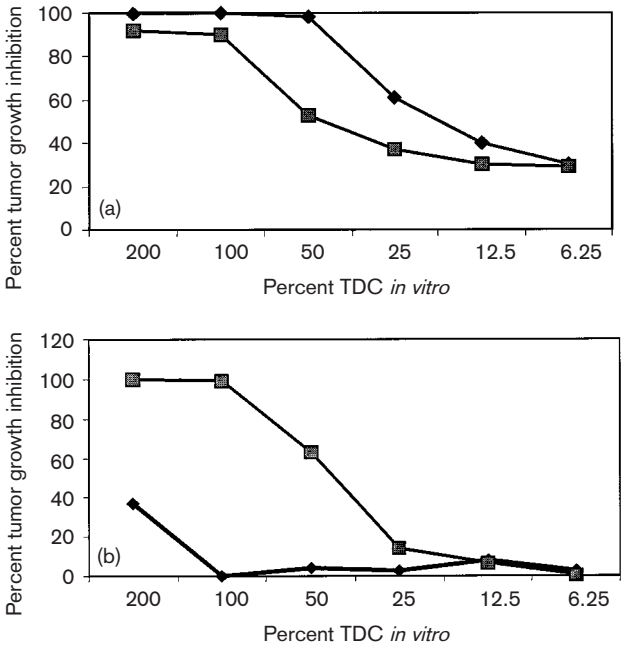

Figure 1. Results of two consecutive *ex vivo* chemosensitivity assays performed in a patient with STS: (a) primary lesion (diamonds, MX+PTX; squares, DOX) and (b) recurrent tumor (diamonds, cisplatin; squares, MX+PTX).

at concentrations above 100% test drug concentration (TDC) referring to the *in vivo* plasma peak. Therefore, the ATP-TCA demonstrated MX/PTX to be an attractive combination for intra-arterial use in this individual patient.

Therefore, the patient was referred to the Department of Radiology, where selective arteriography revealed a good vascularization of the tumor as a major requirement for intra-arterial treatment. Subsequently a biweekly perfusion chemotherapy with MX at 14 mg/m^2 over 1 h preceding PTX at 100 mg/m^2 over 4 h was initiated. Chemotherapy was given via a transfemoral access selectively placed into the right brachial artery. Grade 2 leukopenia, transient grade 1 neuropathy and oncholysis were the only side effects of the treatment. After three cycles, a major regression of the livid nodules and a normalization of the local tumor involvement could be observed clinically. Figure 2(a and b) shows the clinical pre- and post-treatment situation. Magnetic resonance tomography revealed a small hypervascularized residuum located directly proximal of the right ulnar epicondyle. Thus, the patient underwent compartment resection with excision of the suspicious region 1 month after completion of locoregional chemotherapy. Histology failed to detect viable tumor in the excised specimen and thus confirmed complete response. After surgery, the patient received three cycles of i.v. MX/PTX chemotherapy with biweekly MX at 6 mg/m^2 and weekly PTX at 100 mg/m^2 (NT-II). Due to grade 4 leukopenia, the PTX dose was reduced to 80 mg/m^2 for the last course. With this individualized treatment, the complete extremity could be preserved including the entire motoricity. The patient could merely report of reversible sensory disturbances of the terminal phalanges.

Six months later she presented with a tumor relapse located in the right deltoid region outside of the previously perfused area. A new skin biopsy was taken both to confirm histology of recurrent STS and to perform another ATP-TCA. As shown in Figure 1(b), MX/PTX was now compared with cisplatin (CDDP). Whereas the latter failed to exhibit any antineoplastic activity *ex vivo*, the dose–response curve for MX/PTX showed characteristics similiar to the previous one. Again, complete tumor cell kill was induced at high concentrations. Therefore, the decision was made to reinduce the patient with intra-arterial MX/PTX after a nutritive artery was visualized by a new angiography. Another three chemotherapy courses were applied at a biweekly schedule. The dose was reduced to 100 mg/m^2 MX and 80 mg/m^2 due to peripheral neuropathy occuring during the first treatment block. Reinduction chemotherapy was also well tolerated with no signs of systemic side effects. Due to both the patient's age and considerable myelosuppression seen with the first systemic PTX/MX, we abstained from i.v. chemotherapy after completion of the intra-arterial retreatment. Again, clinical complete response was achieved which unfortunately was not confirmed histologically due to the patient's refusal. Nevertheless, the patient remained in good condition and is totally free from STS until today.

Discussion

STS represents a subgroup of very rare angiosarcomas. Due to less invasive surgical and radiotherapeutic procedures, STS has become an occasional but yet life-threatening complication of modern breast cancer therapy. Radical surgery comprising complete amputation or exarticulation of the involved limb is still considered the treatment of choice. However, for the frequent occurrence of distant metastases, mainly located in the lung, mutilating operations are unlikely to improve the prognosis and have thus to be considered palliative. Attempts at limb conservation including local irradiation of locoregional chemotherapy mostly failed and even systemic chemotherapy did not improve the survival rates significantly. Since cure

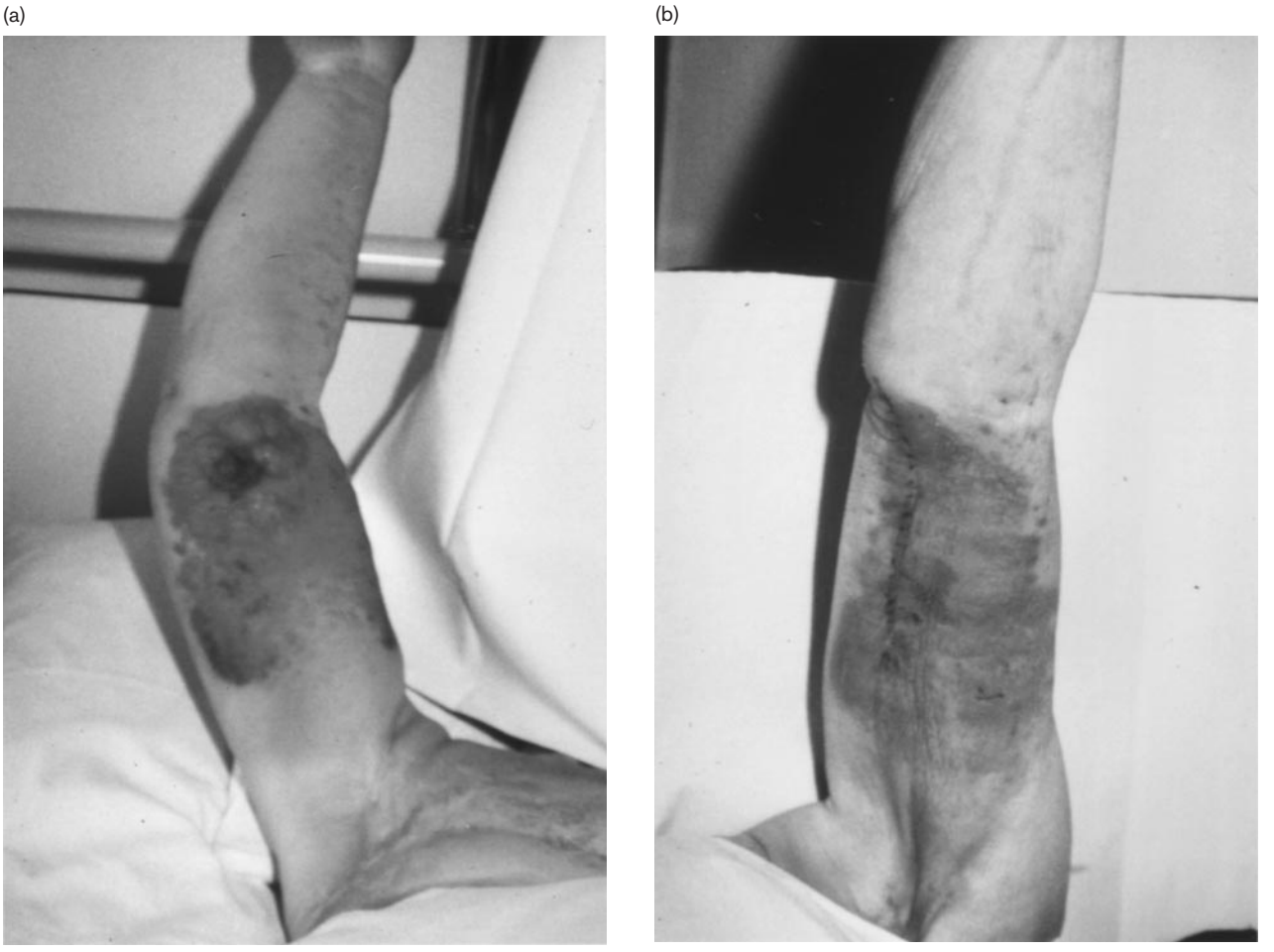

Figure 2. Clinical appearance of STS (a) before and (b) after three courses of intra-arterial MX/PTX.

of STS is a rare event, limb-conserving approaches using locoregional chemotherapy eventually followed by limited surgery and/or irradiation may save quality of life and thus remain an attractive concept in this dismal disease.

Pretherapeutic chemosensitivity testing using the ATP-TCA has provided promising results in both breast and ovarian carcinomas.[6] The assay has been successfully used to select active drugs and combinations in situations where no empirical standard exists, including rare tumors such as choroid melanoma. In order to develop a limb-conserving strategy an individual approach based on the results of ATP-TCA seemed extremely justified in the patient described here.

Recently, DOX has been regarded as the standard drug for intra-arterial administration in soft tissue sarcomas. Nevertheless, its clinical use is severely compromised by both considerable local toxicity and a non-satisfying activity in STS. MX is widely used for both intracavitary and intra-arterial chemotherapy of various neoplasms including breast and ovarian carcinomas. It compares favorably to DOX in terms of both local toxicity and higher local drug concentrations. In heavily pretreated patients suffering from refractory ovarian cancer, the combination of MX and PTX has been found to act synergistically both *ex vivo* and *in vivo*.[7,9] Since PTX provides similar physicochemical characteristics as MX when given intraperitoneally resulting in high local concentrations, the combination was regarded as an ideal intra-arterial regimen. *Ex vivo* ATP-TCA chemosensitivity testing confirmed the superiority of MX/PTX over DOX. In a second specimen assayed 6 months later, MX/PTX was also found to exhibit higher activity compared to cisplatin which is also frequently used for local chemoperfusion. The clinical course of our patient was very encouraging. In accordance to previous reports, we demonstrated that the ATP-TCA can rapidly contribute to planning individual treatment for neoplasms in which no standard therapy exists. To our knowledge, the presented case is the first published example of intra-arterial MX/PTX che-

motherapy. The regimen was well tolerated and highly efficient in this patient and could prevent her from undergoing amputation. As we have demonstrated here, the low local and systemic toxicity of MX/PTX allows retreatment after a relatively short interval without producing cumulative persistant side effects. Limb conservation and, consecutively, preservation of life quality thus appears possible for an extended period of time even when the patient presents with recurrent disease. This promising treatment is strongly recommended to be investigated in a clinical trial with an enlarged number of cancer patients who qualify for intra-arterial chemotherapy.

Acknowledgments

The authors are grateful to Dr T Zirbes (Department of Pathology, University of Cologne Medical Center) for his histological study of this case. We wish to thank Dr Ian A Cree (University College London) for critically revising the manuscript. This work was performed within the framework of the Preclinical Therapeutic Models Group of the European Organizsation of Research and Treatment of Cancer (EORTC).

References

1. Stewart FW, Treves N. Lymphangiosarcoma in post mastectomy lymphedema. A report of six cases in elephantiasis chirurgica. *Cancer* 1948; **1**: 64–81.
2. Woodward AH, Iving JC, Soule EH. Lymphangiosarcoma arising in chronic lymphedematous extremities. *Cancer* 1972; **30**: 562–72.
3. Kindblom LG, Stenman L, *et al*. Morphological and cytogenetic studies of angiosarcoma in Stewart–Treves syndrome. *Virchows Arch* 1991; **419**: 439–45.
4. Malhaire JP, Labat JP, Simon H, *et al*. One case of Stewart–Treves syndrome successfully treated at two years by chemo-therapy and radiation therapy in a 73-year-old woman. *Acta Oncol* 1997; **36**: 442–3.
5. Zylberg L, Picard D, Crick X, Grossin M, Belaich S. Syndrome de Stewart–Treves. Traitement par bleomycine. *Dermatol Venerol* 1992; **119**: 913–5.
6. Kurbacher CM, Cree JK, Bruckner HW, *et al*. Use of an *ex vivo* ATP luminescence assay to direct chemotherapy for recurrent ovarian cancer. *Anti-Cancer Drugs* 1998; **9**: 51–7.
7. Cree JA, Kurbacher CM. Individualizing chemotherapy for solid tumors—is there any alternative? *Anti-Cancer Drugs* 1997; **8**: 541–8.
8. Olmos L, Langier O. Stewart–Treves syndrome. The histopathological evolution of epithelial metastasis. *J Dermatol Surg Oncol* 1997; **3**: 295–301.
9. Chang HAT, Mok KT, Tzeng WS. Induction intraarterial chemotherapy for T4 breast cancer through an implantable port-catheter system. *Am J Clin Oncol* 1997; **20**: 493–9.

(Received 10 February 2000; revised form accepted 24 February 2000)