Sonodynamic and Photodynamic Therapy in Advanced Breast Carcinoma:

A report of Three Cases

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Abstract:

There are increasing data showing that sonodynamic therapy (SDT) is a promising new modality for cancer treatment. Here we report clinical data for 3 advanced refractory breast cancer patients who were treated using a combination of sonodynamic and photodynamic therapy (SPDT), along with conventional therapies. All 3 patients had pathologically proven metastatic breast carcinoma. These widespread carcinomas had ultimately failed to respond to conventional therapy. A sensitizing agent, Sonoflora 1™ (SF1) was taken sublingually, then after a 24h delay, patients were treated with light and ultrasound. Case 1 had left breast carcinoma with widespread metastases. She had been treated with surgery, chemo-, radiation and hormonal therapies, including trastuzumab (Herceptin) and zolodronic acid (Zometa). All conventional treatments failed and the patient, terminally ill, was placed in intensive care. After 3 SPDT treatments in ICU her symptoms improved significantly and trachea, gastric and urinary catheters could be removed. PET/CT scans before and after SPDT treatment showed a partial response (PR). Case 2 had left breast carcinoma with multi-organ metastases. After 2 treatments, PET/CT scans showed a good PR. A PET/CT scan 28 months after treatment failed to detect any tumors. Case 3 had right breast carcinoma with widespread metastases and very poor marrow function. After 2 two treatments, PET/CT scans showed a PR. SPDT with Sonoflora 1™ was well tolerated and had significant therapeutic benefits in some patients with advanced breast cancer. SPDT with Sonoflora 1™ has significant merit for further investigation.

KEYWORDS: chlorophyll derivatives; sonosensitizer, photosensitizer; sonodynamic therapy; photodynamic therapy, breast cancer.

Introduction

Sonodynamic therapy (SDT) is a new modality for cancer treatment that depends on a synergistic effect of tumor-sensitizing drugs and ultrasound. However, few clinical data on SDT has been published in the world literature. One reason is the difficulty of finding a drug suitable for clinical SDT use. Recently a new sensitizer was developed by the late Donald Burke, MD, of Advanced Technologies, Boston, USA. He named it Sonoflora 1™ (SF1). For this study, SF1 was supplied by Advanced Technologies, Boston, Mass., and by its successor company, SonneMed LLC, Marlborough, NH. This agent is a chlorophyll derivative that has very high sonodynamic as well photodynamic activity, with an absorption peak at wavelength 636 nm.

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Embryonic zebra fish assay data provided by Advanced Technologies show no evidence of toxicity. Our animal studies demonstrate that SDT with SF1 does inhibit growth of mouse S-180 sarcoma, even when the tumor was covered by a bone.[2] Here we report initial clinical data using SF1 for sonodynamic and photodynamic therapy (SPDT) in advanced breast carcinoma.

Case presentation

From 2005 to 2007, we consecutively treated 3 advanced breast carcinoma patients using SPDT. All carcinomas were pathologically proven and all patients had failed conventional therapies. SF1 was given to patients through lingual absorption for 2 or 3 days. 24h after taking the last dose of agent, a red LED light, 630 nm and 20mW/cm², was used, irradiating the tumor area or the whole body for 30 minutes (Figure B1, B2 and C). Then a portable ultrasound device was applied, to treat each tumor area for 20 minutes at a 1 MHz frequency and power of 2.0W/cm² (Figure C and E2). The light and ultrasound treatments were performed daily for 3 days. Based on patient situation, one or two weeks later next cycle treatment was repeated. Cases 1 and 2 were given SDT using a conductive gel on the skin (Figure C). Case 3 was given SDT through water (Figure E2).

Case 1, female, aged 43. She had left breast carcinoma resection in March, 1997. Pathological examination confirmed the carcinoma, T2N2M0, with Her-2[++] , P53[-], ER[+++], PR[++] , EGFR[-]. After surgery, she received 6 cycles of chemotherapy (cyclophosphamide + doxorubicin + 5-fluorouracil, CAF), radiation therapy (DT: 50 / GY / 25F), and then tamoxifen (TAM). The cancer recurred in 1999 and had spread throughout the body. She then had radiation therapy, chemotherapy (TF 6 cycles, NVB + Herceptin 6 cycles and Xeloda 6 cycles), hormone therapy (Zoladex and Femara), and ⁸⁹Sr treatment (2 courses). All treatments ultimately failed.

A PET/CT scan in March, 2005 showed that the tumor had spread to bones, lungs, liver and abdomen. The metastases in the neck had already destroyed the cervical vertebra and had involved the spinal cord. (Figure A1). By May, 2005 the patient had high level paraplegia, respiratory failure, heart failure, lung infections, high fever and no feeling in the limbs. Her heart rate was 150 to 170 /min and she had to be put on a respirator to maintain breath. She was terminally ill, and her tumors could not be treated with conventional methods. She was transferred from ICU of another hospital to our hospital for SPDT on May 16, 2005 (Figure A2). Next day, she was treated with SPDT with SF1 30mg plus a half dose of chemotherapy (DCP+ HCPT. DCP is Dicyclo-Platinum, approved in China for use in clinical trials. It’s anticancer activity is similar to DDP, but with fewer side effects). After one cycle of treatment, her breathing was much improved and feeling in the limbs was restored (Figure B1). After two cycles, the tumor in the patient’s neck had shrunk from 13 x 6 cm to 5 x 3cm. The heart rate was now < 100/min and she could breathe without a respirator (Figure B2). After three cycles, her symptoms further improved, with limbs moveable with aesthesis. The respiratory, gastric and urine catheters were all removed. PET-CT scan in August, 2005 showed a partial response, especially in the neck (Figure B3). She only had reversible grade 2 hematological toxicities. She was moved out of the ICU into a general ward. From 3 to 6 months after the treatments the patient’s neck gradually shortened to about 5 cm. The patient was dead by respiratory failure, heart failure, lung infections on November 14, 2005.
Figure A from Case 1, breast carcinoma, female, 43Ys.

A1: PET/CT scan on 3/25/05 showed the tumor had broadly spread in the patient’s body and the metastases in neck already destroyed the cervix vertebra and involved spine cord (see arrow).

A2: a picture showing case 1 treated in ICU. She was unable to talk, move, feel, eat, and even breathe. She had to use a respirator to maintain breath.

Figure B from case 1

B1 The picture shows her second cycle treatment in ICU. She was able to stop use of respirator that had been necessary to maintain breath.

B2 The picture shows third cycle treatment in a LED red light bed. Her symptoms were already much improved.

B3 Comparing PET/CT scans before and after 3 cycle treatment. PET/CT on Aug. 4, 2005 shows positive partial response, especially on the neck.

Case 2, Female, aged 49. The patient found a small mass on her left breast in July, 2005. A needle biopsy proved it to be a breast carcinoma which was ER- and PR+. The PET/CT scan showed the left breast cancer with multi-organ metastases to the axillary lymph nodes, bones, liver and abdominal lymph nodes (Figure D1). From July to August, 2005 patient was treated with three cycles of chemotherapy (first two cycles with TAXOL 240mg+CHPT 30mg+ DCP 600mg, the third cycle with E-ADM 80mg, CTX 0.8 mg, DCP 600mg). In September 2005, a PET/CT scan showed no significant change in the primary tumor, with new metastases suspected. Immediately thereafter, HIFU was used to destroy a big mass in her left liver lobe, and $^{125}$I radio-seeds were implanted into masses in the right liver lobe and in the breast primary tumor. In October and November 2005, she had 2 cycles of SPDT with SF1 60 mg per cycle (Figure C). A PET/CT scan in December 2005 showed a very positive PR. This included improvement in the tumors which were not treated by HIFU and radio-seeds (Figure D2). A PET/CT taken 28 months after SPDT treatment failed to detect any tumor activity (Figure D3).
Case 3, female aged 36. In April, 2003, the patient’s right breast and axillary lymph nodes were surgically removed. Pathology confirmed a carcinoma (T1N1M0) with ER++, PR++, P53+, PCNA+++, C-erbB2-. After surgery, she had radiotherapy (TD=60Gy/F30) and chemotherapy (3 cycles of CAF and 3 cycles of TAX/EPI). Her hematological toxicities were grade 2 to 4. Then she started hormone therapy. A March, 2007 PET/CT scan showed metastases in the liver, lungs and in many bones (Figure E1). She was considered too ill to receive conventional chemotherapy. She was then admitted to this hospital, where she received 3 cycles of $^{125}$I radio-seed implantation combined with local chemo for the tumors in chest, liver, lumbar vertebra, sacrum and pelvis. Her CEA dropped from 39.7 µg/L to 4.90 µg/L, and CA153 from 5000 U/L to 1500 U/L. However, her marrow function deteriorated. On April 22, 2007 her WBC was $2.0 \times 10^9$ / L, HGB $72 \times 10^9$ / L and PLT $48 \times 10^9$ / L. In May she received 2 cycles of SPDT with SF1 60 mg per cycle. The ultrasound treatment was performed in a water pool (Figure E2). After this treatment, her symptoms were
much improved. Less pain, more active lifestyle and better appetite. A PET/CT scan in June, 2007 showed significant tumor inhibition in both the tumors treated with radio-seeds and local chemotherapy, and those only treated with SPDT (Figure F2). Tumor markers and blood routine had improved to CEA 5.81 µg/L, CA153 306.05 U/L, WBC 3.9 x 10^9 / L, HGB 98 x 10^9 / L and PLT 80 x 10^9 / L. They were even better than before SPDT.

**Figure E from Case 3, female, 36Ys.**

**E1** PET/CT taken before SPDT treatment showing right breast cancer with multi-organ metastases including lung, bones, liver and abdomen lymph nodes.

**E2** the picture shows a water pool which was applied for ultrasound treatment in Case 3.

**Figure F from Case 3. Comparing PET/CT before (F1) and after (F2) SPDT.** PET/CT on June 27, 2007 (F2) shows a highly satisfactory therapy.

**Discussion**

Sonodynamic therapy (SDT) is a therapy in which patients ingest a sonosensitizer, a drug which can be activated by ultrasound. The drug is then activated with low intensity ultrasound, producing a cascade of cytotoxic endogenous agents. The therapy is similar to photodynamic therapy, except that the sensitizer is activated by ultrasound rather than by light. The body transmits ultrasound much more efficiently than light, and this is a decisive advantage when treating deeper tumors. There are research data showing that SDT is a
promising new modality for cancer treatment [1, 4-8], but little clinical data on SDT has been published. One reason is the difficulty in finding a drug suitable for clinical use.

A sonosensitizer suitable for clinical SDT use must have following characteristics: 1. No significant toxicity, 2. High tumor selectivity, 3. High clearance rate from normal tissues, 4. High sonosensitivity and 5. Steady chemical composition. Sonoflora™ (SF1) basically fulfills all of the above characteristics. Our animal experimental data indicates that SDT with SF1 does inhibit growth of mouse S-180 sarcoma[2]. In this study the effect of SPDT with SF1 on advanced breast carcinoma was investigated.

From 2005 to 2007 we had consecutively treated three patients with advanced breast carcinoma using sonodynamic and photodynamic therapy (SPDT), along with conventional therapies. An additive effect might be obtained if SDT is combined with PDT [9].

There are data showing that SDT or PDT is synergistic with chemotherapeutic agents [10,11]. Case 1 was safely and effectively treated with SPDT plus a small dose of chemotherapy. The two together produce better outcomes than the two therapies used separately. In our opinion, the good response in case 1 was mainly due to SPDT. The patient had 24 cycles of chemotherapy, but all chemotherapy ultimately failed. During the first three cycles the patient was so ill that we had to treat her in the ICU and give the SPDT mainly on her neck tumors, which were the most dangerous manifestation of the tumor. After 2 cycle treatment the tumors in her neck shrank very significantly (from 13 x 6 cm to 5 x 3cm) and PET/CT scan after 3 cycle showed positive response, especially on the neck.

We got positive results in case 2 and case 3 using two-step therapy, first the debulking of larger tumors, and then SPDT. To debulk larger tumors we used 125I radio-seed implantation and HIFU. Both of them have few side-effects, and each of them is able to destroy local tumor very effectively. In general, the above local treatment reduces the tumor load, but cannot effectively treat widespread metastases. Using same amount of sensitizer the fewer living tumor cells will absorb more sensitizer, enhancing SPDT therapeutic effect. In case 3 the patient still had many metastases untreated in her cervical vertebra, thoracic vertebra and other places after tumor de-bucking. We used a water pool for her almost whole body SDT treatment (Figure F2). Ultrasound conducts very fast and effectively in water. We believe that SDT delivery through water contributed to this patient’s excellent results. We now routinely carry out SDT using water delivery.

In all three cases, SPDT with Sonoflora was well tolerated. Unlike chemo- and radiation therapy, SPDT has almost no toxic effects, nor has it affected marrow and gastrointestinal function, or damage important organs such as the spinal cord, heart, lungs, liver and kidney. All three patients had metastases in the spine, and for case 1, tumors in neck had already involved the spinal cord. In our experience, SPDT is even safer than conventional PDT. The three cases did not have photosensitive dermatitis and not require interventional procedure to introduce optical fibers into the body or tumor, as often is necessary with conventional PDT.

Pain in the tumor regions was the main side effect of SPDT. If the nurse leaves the ultrasound probe in one position, the energy can accumulate in the deep organs, especially in bone. This causes pain. The problem can be largely avoided by using pulsed ultrasound or by constantly moving the ultrasound probe. SPDT induced tumor breakdown can also induce local pain and make patients feel weak and tired. This is not a severe problem, and patients recover in a few days. In case 1 from 3 to 6 months after SPDT treatments the patient’s neck gradually shortened to about 5 cm, then was dead by respiratory failure, heart failure, lung infections. We suspect maybe one reason for her death is cervical vertebra collapse because her cervical vertebra had been seriously destroyed by tumor before SPDT, after SPDT tumor shrunk the bone could not enough restored.

In summary, SPDT with Sonoflora is well tolerated and had significant therapeutic benefits for some patients with advanced breast cancer. SPDT with Sonoflora has significant merit for further investigation.
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