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High-energy Underwater Shock Wave Treatment for Internal Iliac Muscle Metastasis of Prostatic Cancer: A First Clinical Trial

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The first clinical trial of high-energy shock wave (SW) combined with chemotherapy to treat metastasis of prostate cancer in the internal iliac muscle was conducted. The patient, a 57-year-old man, diagnosed as having mucin-producing, poorly differentiated adenocarcinoma of the prostate invading the bladder wall, had been treated by total cystoprostatectomy. Five months later, metastatic tumors were found in the left axillar subcutaneous tissue and the right internal iliac muscles. For the axillar metastasis we performed radiation and left subclavicular arterial infusion of cisplatin 70 mg, THP-adriamycin (THP) 50 mg and methotrexate 50 mg. For the right internal muscular metastasis, 10,000 to 20,000 shots of SW and simultaneous intravenous injection of carboplatin 100 mg and THP 10 mg were carried out. Neither of the tumors decreased in size, but on magnetic resonance images, the SW-treated tumor exhibited a central low-intensity area. The SW-treated tumor was resected and central necrosis and a collection of mucin in the central area were observed. Hormone-resistant prostate cancer is well-known to be a multidrug-resistant tumor. It is noteworthy that SW and chemotherapy induced necrosis in such a refractory cancer without any significant side effects.

Key words: High-energy shock wave — Shock wave — Anti-cancer drug — Human prostate cancer

High-energy underwater shock waves (SW) have been reported to kill tumor cells in suspension and to delay the growth of solid tumors in animal experiments.[1–3] We previously reported that SW treatment of VX2 cancer implanted in the rabbit urinary bladder induced tumor necrosis and decreased the tumor growth. Vascular damage induced by SW in the tumor may be the primary cause of the tumor necrosis.[4, 5] Recently, we observed a synergetic inhibitory effect on tumor growth by SW and THP-adriamycin (THP) or SW and carboplatin (CBDCA) treatments in experimental studies *in vivo*.[6, 7] In the present study we examined the clinical effects of SW treatment against a metastatic tumor of prostatic cancer in the internal iliac muscle. To our knowledge, this is the first clinical trial of such a cancer treatment using SW in the world.

The patient, a 57-year-old man, diagnosed as having mucin-producing, poorly differentiated adenocarcinoma of the prostate invading the bladder wall had been treated by total cystoprostatectomy on January 21, 1993 after neoadjuvant chemo-endocrine therapy. The serum prostate-specific antigen (PSA) value of the patient was within the normal range. Preoperative chemo-endocrine therapy consisted of 2 courses of internal iliac arterial infusion of cisplatin 100 mg and THP 50 mg,[8] and endocrine therapy consisted of 4 months of diethylstilbestrol phosphate 300 mg *per os* per day. The pathological findings of the total cystoprostatectomy specimen revealed no effect of neoadjuvant therapy. Metastatic tumors were found in the left axillar subcutaneous tissue and right internal iliac muscles at the end of June, 1993 without elevation of serum PSA value. Further chemotherapy with 3 courses of VIP (vincristine 1 mg × 6, ifodfamide 30 mg × 9, peplomycin 5 mg × 18)[9] and endocrine therapy from June 30 to September 12 failed to reduce the size of these tumors.

For the left axillar metastatic tumor (40 × 35 mm in size), 60 Gy of irradiation was performed from October 19 to December 6, and intra-arterial infusions of cisplatin 70 mg, THP 50 mg, and methotrexate 50 mg to the left subclavicular artery were administrated on October 27.

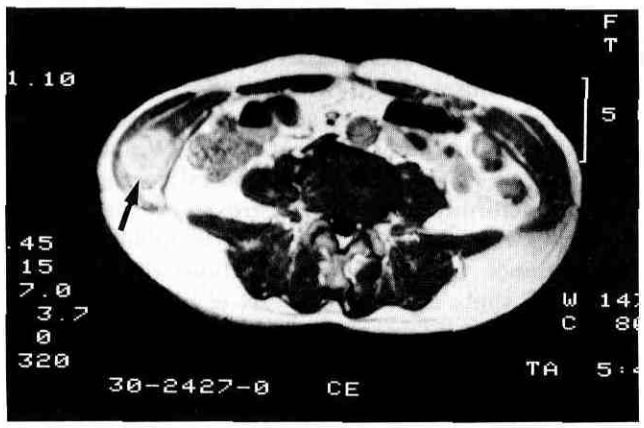
For the right internal muscular metastatic tumor (30 × 25 mm in size), we also attempted combined therapy of radiation and intra-arterial infusion chemotherapy, but we could not find any feeder artery to the tumor. Therefore, we decided to try SW treatment combined with chemotherapy. The patient gave his consent after having been informed about the experimental nature of SW-treatment, which was approved by the Ethical Committee, Tohoku University School of Medicine, Sendai. A series of 10,000–20,000 shots of SW and simultaneous intravenous injection of CBDCA 100 mg and THP 10 mg was completed.

SW exposure: The tumor, under visualization by ultrasound, was exposed to focused SW, which was generated

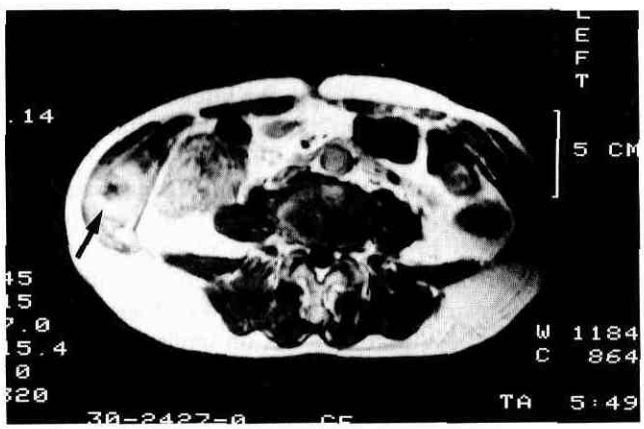
by a 24-piece piezo ceramic of 300 mm aperture with a $2\times2\times19$ mm focus zone and about 100 MPa peak pressure, at a shot-rate of 5 shots per second, using a specially designed treatment apparatus constructed by Toshiba Corporation, Tokyo.[5] SW and chemotherapy were initiated on November 24, 1993 and performed every other day for a total of 4 times under lumbar anesthesia.

Based on magnetic resonance imaging (MRI), the left axillar tumor was heterogenously changed. The SW-treated right internal iliac tumor was also changed, especially in the central region, after the series of 4 SW exposures with chemotherapy, and central necrosis was suspected (Fig. 1). Additional series of SW exposures and chemotherapy induced no further change. The tumor was resected on February 22, 1994 and was cut into 5 mm step-sectioned specimens. The cut surface of the SW-exposed tumor showed a mesh-like structure, and cystic and homogenous areas were positive for PAS staining (Fig. 2).

Histopathology revealed a marked reduction of tumor cells mainly in the central area, associated with fibrous network structures (Fig. 3a). The cystic lesion showed a mucin lake clearly stained by PAS (Fig. 3b). Granulomatous lesions were observed in the fibrous area; macrophages had gathered and the cancer cells had been phagocytized by the macrophages without digestion of the mucin (data not shown). The central low-density area on the MRI may correspond to this mucinous area. If the mucin had been digested, tumor regression might have been observed. Vivid carcinoma cells still remained at the peripheral area of the tumor (Fig. 3c). These vivid carcinoma cells and the mucin were not stained by PAS immunostaining (data not shown).



pre-treatment(11/19/93)



post-treatment(12/24/93)

Fig. 1. Representative pictures of gadolinium-DTPA-enhanced T1-weighted image of right internal iliac tumor pre- and post-treatment with SW and chemotherapy. A lower signal intensity in the central area (arrow) may be due to central necrosis.

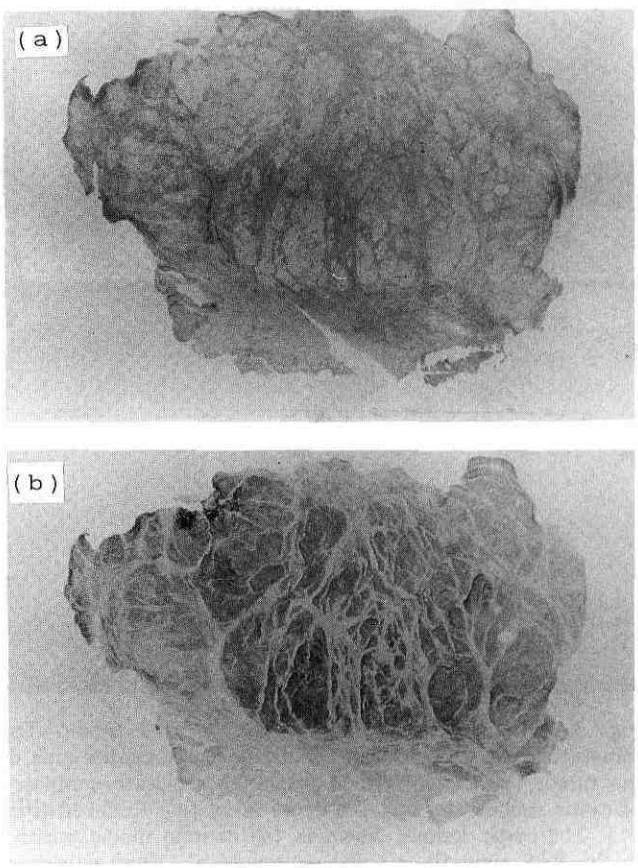


Fig. 2. The cut surface of the SW-exposed tumor showed a mesh-like structure (a), and the cystic and homogenous lesions were positive for PAS staining (b). Reduced from $\times3.5$.

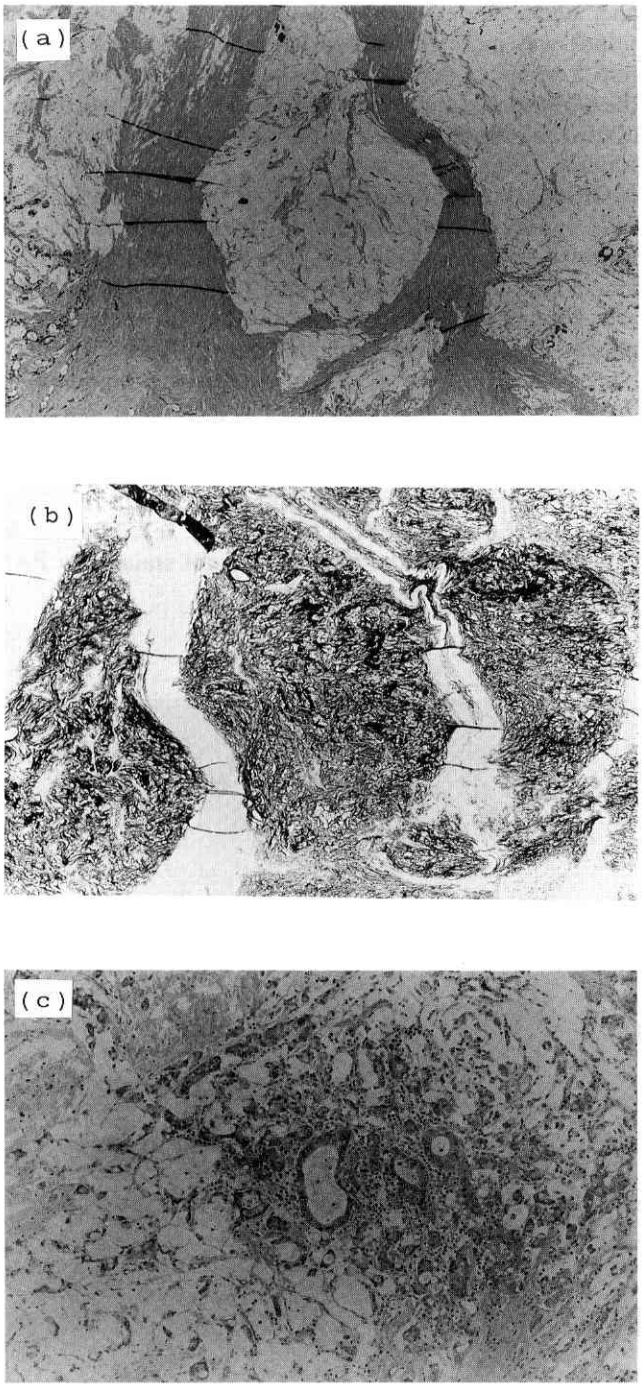


Fig. 3. Microscopic findings of the resected tumor. The tumor cells are decreased in cellularity in the central area of the tumor, associated with a mesh-like structure composed of cystic lesions and collagen-dense areas (a). Reduced from ×5. The cystic lesions shown in (a) contain mucin positive to the PAS stain (b, a serial section to a). Vivid adenocarcinoma cells, characteristic of tubular structure with mucin production, remain at the peripheral area of the tumor (c). Reduced from ×10.

A total of eight SW exposures of 10,000 to 20,000 shots produced no side effect except for minimal small subcutaneous bleeding spots in the SW-exposed area. Subcutaneous bleeding was minimized after the repeated SW exposures. The patient complained of pain in the area exposed to SW and an oral anodyne was necessary. Laboratory data revealed no particular change except for a temporary elevation of creatine kinase, which was probably caused by muscle destruction in the SW-exposed area (Fig. 4).

The right axillar tumor could not be resected because the brachial nerve was involved in the tumor.

As of October 31, 1994, the patient is well and subclavicular arterial infusion chemotherapy is being continued for the left axillar metastasis. No other metastatic sites have been detected, indicating that SW did not induce dissemination or metastasis.

SW has been reported to suppress tumor growth *in vitro* and *in vivo* in several experimental systems, but the precise mechanism of its destructive effect on cancer cells is still unknown. Kohri *et al.* observed destruction of microvilli on the tumor cell surface by SW and swollen mitochondria *in vitro* under electron microscopy.[10] We observed deformed nuclei and destroyed organella of the implanted VX2 bladder cancer cells in rabbits and the disappearance of intercellular junctions of these cells after 1000 shots of SW.[11] Ellwart *et al.* reported that microcavitation might cause damage to the cell membrane.[12] By ultrasound analysis, a hyperechoic region in the living tissue was observed in the SW-focused area, and this was thought to be due to the cavitation bubbles. Similar cavitation bubbles and hyperechoic change of the tumor were detected in our present treatment, but the area of the cavitation bubbles was larger and wider, and the necrotic area of tumor tissue was wider and deeper in our previous rabbit bladder cancer model than in our present treatment. Accordingly the intensity of the cavitation bubbles may reflect the degree of tumor tissue damage.

Cisplatin has been used as a combined treatment with SW.[3] On the other hand, CBDCA, generally accepted as one of the most promising analogs of cisplatin with a definite therapeutic activity against several tumors, is less toxic than cisplatin to renal tubules. We observed a synergetic effect of SW and CBDCA on implanted subcutaneous carcinoma in mice.[7] Since we have already demonstrated the combined effect of SW and THP on rabbit bladder cancer,[6] we decided to employ a combination therapy of SW, CBDCA and THP in the present case.

We observed that SW induced vascular damage in the tumor, and Gamarra *et al.* observed a reduction of blood flow in tumors of golden hamster bearing amelanotic melanomas in the dorsal skin after 200 shots of shock wave exposure.[13] Although we observed a synergetic

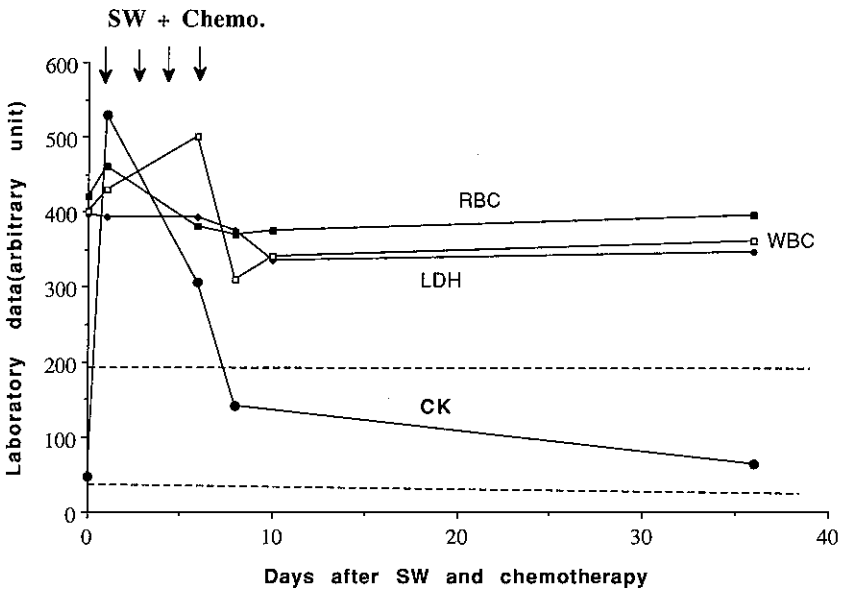


Fig. 4. Shock wave treatment and change of the laboratory data. Laboratory data showed no particular change except for the temporary elevation of creatine kinase (CK), possibly due to muscle destruction by SW. Laboratory data are expressed in arbitrary unit: RBC$\times 10^4/\mu$l (■, normal range: 429–577), WBC$\times 10/\mu$l (□, normal range: 340–940), LDH IU/liter (◆, normal range: 198–424) and CK IU/liter (●, normal range: 50–197), respectively.

effect of SW and THP, the concentration of THP of the SW-treated tumor was lower than that of the unshocked control.[14] Therefore, to induce wider tumor necrosis, the relationship between the amount of SW exposure and drug concentration, and suitable timing for drug administration should be further studied.

Steinbach and Hofstadter examined combined SW and anti-cancer drug therapy *in vitro*, to determine the best protocol, that is, which was more effective, drug administration before, after or during SW, and concluded that drug administration during SW was the best to suppress cancer cell growth.[15]

Accordingly the combined effects of SW and cytotoxic or cytostatic drugs should be examined further not only *in vitro*, but also *in vivo*.

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