Special Edition I

Potential of Hyperthermic Effects Using Hydralazine

Takeo Hasegawa Ph. D.¹⁾, Tatumi Ishiguro B. S.²⁾,
Taichi Oshima M. D.³⁾, and Yoshimasa Tanaka M. D.³⁾

- 1) Department of Radiological Technology, Suzuka University of Medical Science and Technology, Suzuka Mie 510-02.
- 2) Department of Radiology, Daiori Medical Center of Osaka Textile Health Insurance Organization, Osaka 559.
- 3) Department of Radiology, Kansai Medical University Moriguchi city OSAKA 570.

Abstract : It is said that the efficacy of hyperthermia for malignancies depend on various vasophysiological factors in the tumor, such as pH, blood flow and oxygen tension (pO₂). The present animal experiment was performed to ascertain how the effect of hyperthermia can be enhanced by administration of hydralazine (HYD), a vasodilator, which is known to decrease the local blood flow selectively and accordingly, decelerate thermal diffusion in the tumor. HYD (2-5mg/kg) was injected intraperitoneally 20 min before hyperthermia, which was done for 20-30 min at 43°C by the use of a thermo-static water bath. The tumor quadrupling time was 4.5 days in the untreated FM3A group, 5.4 days in the HYD treated FM3A group, 8.5 days in the heat alone FM3A group and 11.2 days in the HYD plus heat treated FM3A group. Those in the respective SCC-VII group were 7.7 days, 9.0 days, 11.1 days and 14.0 days. The enhancement ratio was 2.48 in the treatment for FM3A tumor and 1.81 in the treatment for SCC-VII tumor. Thus, these results indicate that HYD can increase the therapeutic efficiency of local hyperthermia treatment by inducing the change of microenvironment i. e. low pH, tumor hypoxia, deficient nutrition secondary to blood flow diminution which increase the sensitivity of tumor to heat.

Key words : Hyperthermia, Blood Flow, Vasodilator, In vivo.

I . Introduction

Changes in tissue blood flow is related to thermo-diffusion due to blood circulation, tissue oxygen tension and nutritional condition. Therefore, therapeutic gain by hyperthermia and

radiation therapy for malignant tumors depends largely upon these factors^{1) 2) 3) 4)}. It is known that tumors in general have a necrotic area of the center and its periphery is in a hypoxic state because of a low blood flow⁵⁾. This area is not easily accessible to anti-cancer drugs, in addition, the hypoxic condition makes those lesions tolerant to chemotherapy and radiotherapy. In this study we confirmed that the anti-tumor effect of hyperthermia was enhanced by hydralazine (HYD) as a vasodilator. HYD dilates normal blood vessels, which have smooth muscle, thereby increasing the blood flow of normal tissues. However, tumor vessels are poorly responsive to the drug because of the scarcity of local blood flow, so that the local blood flow is reduced by a steal effect following HYD administration⁶⁾. It is surmised, therefore, that HYD administration leads to the decrease of blood flow and the aggravation of the nutritional condition, and the cytotoxicity of hyperthermia is augmented and, at the same time, the ability to repair hyperthermia induced damage.

II. Materials and Methods

Four week old male C3H mice were used. The tumor cell lines used were FM3A and SCC-VII. These cells ($5 \times 10^5 - 2 \times 10^6$ cells/0.05ml) were transplanted into the femoral subcutis. The experiment was started 10 days after transplantation when the tumor grew to 7 mm in diameter. An appropriate amount of HYD to make a dose of 1 mg/kg, 2.5 mg/kg, or 5 mg/kg was dissolved in 0.3 ml of physiological saline and administered into the peritoneal cavity. HYD was injected intraperitoneally 20 min before hyperthermia, which was done for 20-30 min at 43°C by the use of a thermo-static water bath. Tumor sizes were measured three times a week and volumetry was performed according to the formula; $\pi abc/6$, where a, b and c indicate three perpendicular diameter. Time-course changes in local blood flow were monitored by use of a laser doppler flow-meter (ALF 21, Advance) and a special sensor (500 μ m in outer diameter) inserted into the tumor. The tissue oxygen tension (pO₂) was measured by polarographic method. The blood flow distribution within the tumor was studied in the following manner: Hoechst-33342, a fluorescence dye (excitation = 352 nm,

Normal tissue did not show the decrease of blood flow after HYD infusion. But tumor tissue shown the decrease of blood flow significantly.

Fig. 1 Changes in blood flow in SCC-VII tumor (●) and intact muscle (○) after infusion of hydralazine (HYD).

Fig. 2 Fluorescences showing blood distributions in FM3A and SCC-VII tumors after injection of hoechst-33342.

emission=460 nm, dose=50 $\mu\text{g/g}$), was infused into the tail vein and the animal was sacrificed by cervical dislocation 3 min later. Immediately thereafter, the tumor was surgically taken out and freezed at -70°C . The freezed tissue block was sliced into sections 10 μm in thickness and the fluorensce distribution in the tissue was examined under a fluorescence microscope.

III. Results

Fig. 1 illustrates the normal tissue and tumor tissue of blood flow after HYD injection. The blood flow did not show the big changes in the intact musular tissue after HYD administration. In contrast, notable decreases in blood flow were recognized at all places within the tumor except for the necrosis area. An examination of the blood distribution using Hoechst-33342 revealed that the fluorescence intensity was significantly lowered in either the FM3A and the SCC-VII tumor after HYD injection. The blood flow and the oxygen tension were shown same tendency when compared with normal tissue and tumor tissue. This suggested that the local blood was markedly decreased by HYD administration (Fig. 2). This observation substantiated the HYD induced reduction in local blood flow. The tumor quadruping time was 4.5 days in the untreated FM3A group (control), 5.4 days in the HYD-treated FM3A group, 8.5 days in the heat treated FM3A, and 11.2 days in the HYD plus

Fig. 3 FM3A tumor growth curves after various treatments. Each point represents a mean of determinations in 7 mice. Hyperthermia was given 20 min after injection of hydralazine (5mg/kg).

Fig. 4 SCC-VII tumor growth curves after various treatments. Each point represents a mean of determinations in 7 mice. Hyperthermia was given 20 min after injection of hydralazine (5mg/kg).

heat treated FM3A group (Fig. 3).

Those in the respective SCC-VII groups were 7.7 days, 9.0 days, 11.1 days, and 14.0 days (Fig. 4). There was a correlation between the enhancement ratio and the degree of reduction in blood flow after HYD administration. To sum up, our findings suggest that HYD exerts a stealing effect, thereby decreasing blood flow in the tumor and promoting the carci-no-static effect of hyperthermia. If the side effects of HYD can be diminished, its clinical application as an adjuvant to hyperthermia seems promising.

IV. Discussion

Since it has a vasodilator action, it has long been utilized clinically as an anti-hypertensive drug. Pharmacokinetic studies have demonstrated that it acts on the enzyme system of the arteriolar smooth muscles, thereby dilating the vessels, and that it is catabolized by the mediation of N-acetyltransferase⁷⁾. HYD induces vasodilution in normal tissues with smooth muscles, whereas it fails to do so in tumors which are deficient in smooth muscles. In normal tissues, therefore, the blood flow increases after HYD administration.

However, in tumor scarce of blood flow, nutrition and oxygen deliveries are deficient and the low blood flow area and hypoxic area increases, which results in a enhancement of the cytotoxicity of hyperthermia⁶⁾. Besides, HYD is said to reduce tumor tissue blood flow selectively⁸⁾. Some investigators used it in an attempt to enhance the efficacy of hyperther-

mia for malignancies whose thermo-distribution was reduced⁹⁾. A reasonable inference from the foregoing is that HYD administration might be useful adjuvant to cancer therapy using a hyperthermia on condition that it is essential to find an optimum dose in consideration of the adverse drug reactions and adequate counter measures that can taken.

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