

HYPERTHERMIA AND CANCER

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HISTORICAL DEVELOPMENT: The use of hyperthermia (heat) in the treatment of malignant tumors is as old as medicine itself. For example, the 5000-year old Edwin Smith Surgical Papyrus mentions heat as potential treatment for breast cancer [1]. Hippocrates, the father of medicine, proposed that surface tumors should be cauterized by application of hot iron. In modern times, more advanced methods (hot water bath, pyrogens such as mixed bacterial toxins, perfusion heating, high frequency radiation, magnetic fluid hyperthermia) were employed to heat, and hopefully destroy, tumors.

Use of hyperthermia in cancer patients is based on two different principles. Mild hyperthermia (up to 42°C) is used to stimulate the immune response for non-specific immunotherapy of cancers. Higher temperatures (around 45°C) are used with the hope of inducing regression or outright disappearance of the cancer by direct cell destruction with heat. Unfortunately, the use of hyperthermia by itself to control malignant tumors under clinical conditions has proved to be an elusive goal. In part, this was due to the difficulties encountered in delivering sufficient thermal energy to cancer cells. Whole-body heating could overcome this problem, but the temperatures required to kill cancer cells by heat alone are usually higher than can be tolerated by normal body tissues.

To overcome these limitations, attempts have been made to use hyperthermia in combination with other treatment modalities such as chemotherapy and radiation therapy [1]. This approach was based on growing knowledge about microenvironmental conditions within the tumor, in particular the fact that many tumors contain a significant fraction of hypoxic (poorly oxygenated) cells. Hypoxic cells are much more resistant to radiation than euoxic (well oxygenated) cells, so the presence of hypoxic cells in tumors may constitute a major obstacle to successful radiation therapy of cancers. For heat the situation is reversed, that is, hypoxic cells are more heat-sensitive than euoxic cells. Therefore, it seemed logical to combine these two modalities in cancer therapy.

WORK IN OUR LABORATORY: Based on the principles outlined above, we developed and tested a combination technique where hyperthermia is used in conjunction with chemical agents that enhance the radiation response of cancers [2].

We had previously shown that radiation exposures of cancer cells at temperatures of 41°C or higher resulted in strongly enhanced tumor cells death. Figure 1 shows the results of an experiment where euoxic and hypoxic BP-8 murine sarcoma cells grown in mice were irradiated at normal (37°C) or elevated (41.5°C) body temperatures. In this study, whole-body heating was performed by placing the mice in perforated plastic holders and immersing them for 1 h in a precision-controlled water bath. Hypoxic cells exhibited significantly greater heat enhancement of radiation death than euoxic cells. With euoxic cells the D_0

(the dose that reduces cell survival along the exponential part of the survival curve to 37% of the control value) was 1.8 Gy at 37°C and 1.4 Gy at 41.5°C, yielding a DMF (dose modifying factor, that is, the ratio of the two D_0 values) of 1.29. With hypoxic cells the D_0 declined from 5.2 to 3.0 Gy (DMF 1.73). The oxygen enhancement ratio (the ratio of the D_0 values for euoxic vs. hypoxic cells) was 2.89. Thus, heating at 41.5°C was effective in enhancing radiation-induced cell death in hypoxic cancer cells, but not as effective as full oxygenation.

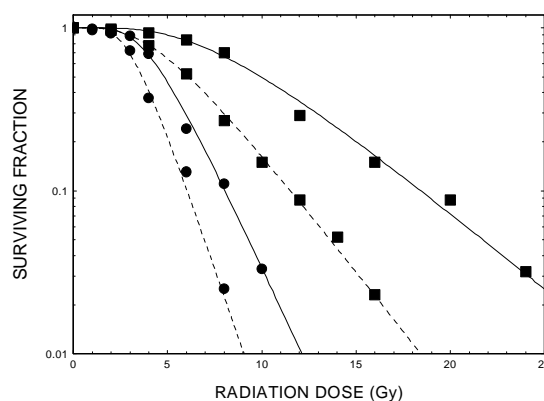


Fig. 1: X-ray response of euoxic (circles) and hypoxic (squares) BP-8 murine sarcoma cells irradiated at either 37°C (solid lines) or 41.5°C (dashed lines).

In another series of radiosensitization experiments, euoxic and hypoxic BP-8 cells were irradiated at 37°C in the presence or absence of misonidazole, a chemical radiosensitizer that mimics the action of oxygen. As illustrated in Figure 2, administration of misonidazole (0.5 mg/g body weight) had little effect on the radiation response of euoxic cells (DMF of 1.13), but did reduce the D_0 of hypoxic cells from 5.2 Gy to 2.4 Gy (DMF of 2.17).

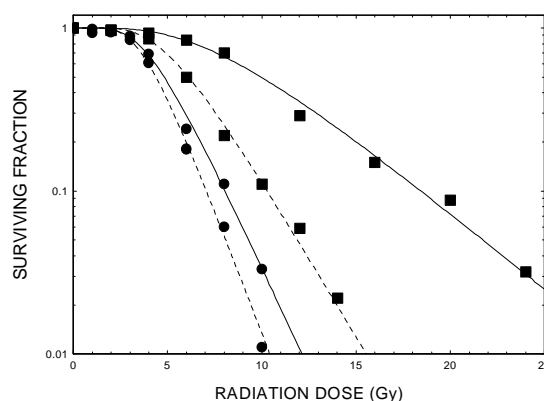


Fig. 2: X-ray response of euoxic (circles) and hypoxic (squares) BP-8 murine sarcoma cells. Solid lines show the radiation response of control groups, dashed lines the response of misonidazole groups.

From the data in Figures 1 and 2 it is apparent that heat and misonidazole are effective in potentiating radiation death in hypoxic cancer cells, but neither mode of

radiosensitization is as effective as full tumor oxygenation. However, when the two agents are used in combination with each other, they produce synergistic potentiation effects on hypoxic cells that far exceed the action of oxygen. As shown by the data in Figure 3, the D_0 of hypoxic BP-8 cells subjected to heat and misonidazole during irradiation was reduced from 5.2 Gy to 1.2 Gy (DMF of 4.33). In other words, the degree of radiosensitization by combination treatment was such that the hypoxic cancer cells actually became more radiosensitive than euoxic cells. Even euoxic cells subjected to combination therapy were not as radiosensitive as hypoxic cells irradiated in the presence of heat and misonidazole. Similar results were obtained with other tumors (Figure 4), so it would appear that synergistic radiosensitization of hypoxic cancers by combination therapy may be a general phenomenon, not a unique event observed only in BP-8 murine sarcoma [2].

However, no radiosensitizer (or combination of sensitizers) will be of any clinical value unless it can be shown that normal body tissues are not sensitized to the same extent as tumors. Lethality experiments on mice and studies on three normal body tissues (Table 1 and Figure 5) indicated that radiosensitization by combination treatment was relatively minor or completely absent in normal tissues of mice (DMF of 1.3 for skin, 1.0 for bone marrow and intestine). These results suggest that simultaneous administration of hyperthermia and oxidizing agents should be an effective adjuvant for clinical radiation therapy of cancers.

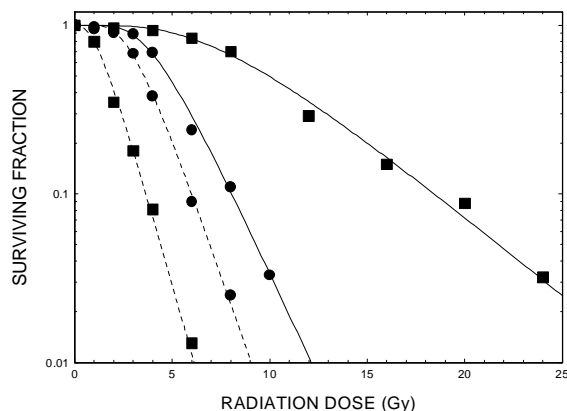


Fig. 3: X-ray response of euoxic (circles) and hypoxic (squares) BP-8 murine sarcoma cells. Solid lines show the response of control groups, dashed lines the response of euoxic and hypoxic cells subjected to heat and misonidazole.

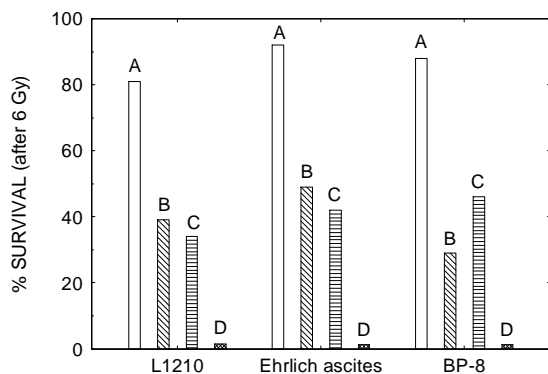


Fig. 4: Radiation response of hypoxic L1210, Ehrlich ascites and BP-8 cells after exposure to 6 Gy under the following conditions: A: 37°C, no misonidazole; B: hyperthermia (41.5°C for L1210 and Ehrlich ascites, 42°C for BP-8), no misonidazole; C: 37°C, misonidazole; D: 41.5°C, misonidazole.

CLINICAL CONSIDERATIONS: The findings reported above were subsequently confirmed by three other laboratories working on a variety of different tumor systems. Thus, there is no longer any doubt that combination therapy does in fact yield radiosensitization effects that exceed those of oxygen. The sensitization effects are selective for hypoxic cancers, that is, normal body tissues are not sensitized to the same extent.

Table 1: LD₅₀₍₃₀₎ (lethal dose to 50% of the mice within 30 days after radiation exposure) for ICR mice irradiated at 37°C or 41.5°C in the absence or presence of misonidazole.

Treatment	LD ₅₀₍₃₀₎ (Gy)
Control (37°C, no Misonidazole)	5.6
Heat (41.5°C, no Misonidazole)	5.5
Misonidazole (0.5 mg/g, no Heat)	5.5
Heat plus Misonidazole	5.4

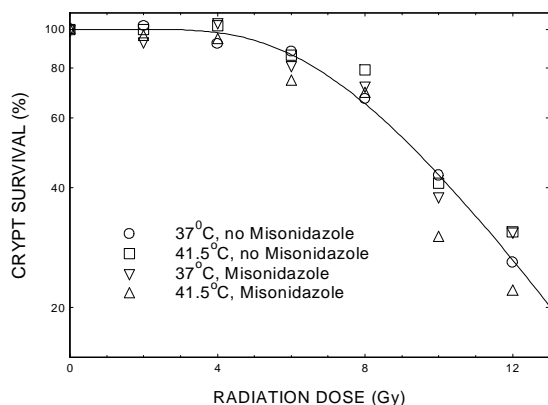


Fig. 5: Radiation response of the intestine after whole body irradiation of mice at 37°C or 41.5°C with or without misonidazole. The percent figures refer to percent survival of the intestinal crypts after radiation exposure.

In spite of enormous magnitude of the sensitization obtained in mice, at least two improvements are required before this treatment regimen can be used in clinical radiotherapy. First, we need better methods for selective tumor heating. The studies described above were performed on mice that were subjected to whole-body heating in a water bath. This is not optimal for clinical application because whole-body heating limits the heat dose that can be given to the cancer. It seems likely that the hyperthermia component of combination therapy can be significantly improved by heating tumors selectively with magnetic particles subjected to external AC magnetic fields.

A second important improvement would be the development of a more selective method of drug delivery into the tumor. Nitroimidazoles such as metronidazole and misonidazole are usually well tolerated in mice, but clinical use of these agents in human patients can result in severe peripheral neuropathy. One promising approach to deal with this obstacle is to encapsulate the radiosensitizing agents in heat-sensitive liposomes [3]. Ideally, the liposomes should also contain magnetic particles, so they can be guided to the tumor by a magnetic field. After the liposomes reach the interior of the tumor, they could be subjected to heating by an external AC magnetic field [4]. This would cause the liposomes to burst and selectively release the radiosensitizing agent in the interior of the tumor. Such a system may also facilitate selective local

tumor heating. If successful, this procedure could offer an elegant method to realize the promise of combination radiosensitization in the clinical radiotherapy of cancers.

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