The Activation of Immunological Activity and Anti-tumor Effects by Mild Hyperthermia

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Abstract : It is believed that hyperthermia will show anti-tumor effects at the temperature over 42.5 degrees. But we found that the mild hyperthermia as under 42.5 degrees still shows anti-tumor effects due to the immunological activity. We used C3H mice bearing SCC-VII tumor. These mice were heated at the temperature of 39-41 degrees by 1 hour in controlled water bath. After giving mild hyperthermia, white blood cells (WBC), lymphocyte cells (LyC), NK cell activity were increased compared with pre-heat condition. The delays of the SCC-VII tumor growth in C3H mice was observed after mild-hyperthermia. It shows that the immunological activity were increased as activated WBC, LyC and NK cells. Also anti-tumor effects were produced by mild hyperthermia. It is supposed that quantitative stimulation of femoral region by mild hyperthermia has induced the activation of hemopoietic organs in bone marrow of femoral region and this has activated immunological potency, mild hyperthermia seems to be a useful and effective auxiliary therapy which is not only effective for the treatment of malignant tumors but also for the treatment of diseases related to immunological activity (e. g. viral hepatitis type C, collagen diseases, AIDS, postoperative physical restraint, auxiliary therapy during thermotherapy, elimination of immunodeficiency, etc.).

Introduction

Hyperthermia is a general name for therapeutic methods to treat by raising temperature in human body. This includes the therapy to improve vascular circulation in various types of organs using infrared ray lamp or ultra-short wave therapy device, and folk remedy therapy such as hot-spring cure. In general, however, the term hyperthermia is applied for the therapeutic method for the treatment of cancer.
using micro wave, RF wave thermal system or intra-tissue thermal device. In 19th century, Busch reported the reduction in size of tumors on the faces of the patients with erysipelas with high fever \(^1\). Coley described that cancer can be treated through infection of Streptococcus pyrogenes, or that a therapy to induce high temperature by giving an extract of pyrogenic toxin or pyrotoxin to the patients with cancer has provided effects \(^2\). In 20\(^{th}\) century, however, attention has been focused on other therapeutic methods such as surgical treatment or chemotherapy. More recently, attention has been paid again on pyrogenic toxin. It was found to be a tumor necrosis factor (TNF), which is one of cytokines secreted by macrophages \(^4\). Science 1960’s, fervent attempts have been made on fundamental research of hyperthermia. With remarkable progress in the instruments and technique in recent years, fundamental and clinical research showed extensive development \(^9\). At present, hyperthermia is clinically very important as interdisciplinary therapeutic method, and studies are being performed on combined effects with surgical treatment, radiotherapy, chemotherapy and gene therapy for the treatment of malignant tumor \(^4-8\). Also, hyperthermia is characterized by its selective thermal effect on tumor \(^9-10\). Special features of the hyperthermia are as follows: The thermal treatment device is available at relatively low cost and is much easier to handle and manage compared with the radiotherapy devices \(^9\). Hyperthermal effects rapidly increase when temperature is increased only by 1°C. from 42.5°C \(^9\). Hypoxic tissues resistant to radiotherapy have high thermo sensitivity \(^\(11\)\) \(^17\). The tissues under poor nutrition are highly thermsensitive \(^13\). The tissues with low pH value are thermosensitive \(^14\). The cells in S period in cell cycle have higher thermsensitivity \(^15\). Hyperthermia reduces restoration of potential lethal effect in the cells induced by radioactivity \(^17\). The tissues with higher temperature increasing ratio have higher thermsensitivity \(^10\). Vasoactive substances can increase thermal effects \(^19\) \(^20\). Further, indication of hyperthermia can be expanded to various cases by changing the procedure to add physical thermal energy. In some cases, however, it is difficult to increase the temperature of the region under treatment to 42.5°C or higher. In case of systemic hyperthermia, heating procedure at relatively mild temperature and slow rate is often adopted. This is because adverse effect by heating may be propagated to the whole body otherwise or because temperature limit for human body is 42°C. In this sense, it is called mild hyperthermia. There have been not many reports, which described mild hyperthermia for the purpose of treating the cases with cancer. Among them, there are reports describing the possibility of involvement of immunological response of cytokines, while most of the studies have their purposes to investigate systemic hyperthermia as heat inducing element \(^21-30\). However, there are other reports: a report demonstrating the activation of TNF \(^29\), or a report on the activation of macrophages in vitro by hyperthermia \(^31\). This suggests the possibility of immunological response by heating relatively mild temperature (39°C - 42°C). In this respect, by experiments using mouse as model, we evaluated the effects of hyperthermia under temperature of 42.5°C and lower and demonstrated that the activation of immunological response is increased and anti-tumor effect can be obtained. The results of our study are reported.

Materials and methods

1) Transplantation of tumor

For the experiments, 10-15 C3H/HeJ mice (male; 6-week-old) were used for each treatment groups.
To each animal, SCC-VII tumor was transplanted subcutaneously in femoral region. For tumor transplantation, SCC-VII tumor cells were used, which had been cultured in about 50 ml of culture solution (30% FCS ; 10% MEM) placed in a Petri dish of 10 cm in diameter. The proliferated and attached tumor cells were removed and placed by pipetting into 0.25% Trypsin solution (sterile PBS buffer solution). The cells were washed twice with PBS buffer solution and were counted. Trypan blue stain solution (mixture of 0.025% Trypan blue and 4.25% NaCl at mixing ration of 4 : 1) was mixed with cell suspension of the same volume. Vital cells not count was adjusted to $5 \times 10^5$ cells/0.05 ml, and this was injected subcutaneously in femoral region. After transplantation, when the tumor has grown to 4 - 5 mm in diameter, the experiment was started.

2) Thermal treatment at 39.0 °C and 41.0 °C

Each of the C3H/HeJ mice with SCC-VII tumor transplanted subcutaneously in femoral region was fixed on an acrylic fixture. Pentobarbital (50 mg/kg) was given intraperitoneally, and the animal was anesthetized. With 10 mice in each group, only femoral region of each mouse was immersed in two different types of warm water tanks (water tanks with temperature controlled to 39.0°C and 41.0 °C for 60 minutes respectively). After the treatment, the animals were divided into 4 groups. Group 1 was used for blood cell measurement, and blood was collected periodically from vein in tail. Group 2 was used for the preparation of tumor growth curve. Group 3 was classified for the measurement of NK cell activity. Group 4 was used as control without treating with hyperthermia therapy.

3) Thermal treatment before and after tumor transplantation

Mice were divided in the following groups with 15 mice in each group: a group treated with thermal treatment 12 hours after SCC-VII tumor was transplanted subcutaneously in femoral region ($5 \times 10^5$ cells/0.05 ml) 12 hours after the thermal treatment (41°C ; 60 minutes), a control group transplanted with SCC-VII tumor ($5 \times 10^5$ cells/0.05 ml) and without thermal treatment. Then, NK cell activity and relative tumor volume were determined.

4) Thermal treatment every day and thermal treatment every other day

Each of the C3H/HeJ mice (male ; 7-week-old) transplanted with SCC-VII tumor subcutaneously in femoral region was fixed on acrylic fixture using adhesive tape. Pentobarbital (50 mg/kg) was given intraperitoneally to induce anesthesia. Then, the animals were divided to 10 mice in each group, and only femoral region was immersed in warm water tank, and thermal treatment was carried out. Thermal treatment was performed at 41.0 °C for 30 minutes, and on every other day for two groups, and five sessions of treatment were performed. After the first hyperthermia, relative tumor volume was determined.

5) Blood cell counts

Each mouse was fixed on an acrylic fixture (with mouse body fixed in a tube with only its tail projected outward). From each mouse in the 39.0°C group, the 40.0°C group, and no treatment group, 10 µl of blood was collected from tail vein using infection needle and fine glass tube. To avoid
accumulation of WBC due to wound, blood was collected from tip of tail toward root of tail. After blood collecting, the collected site was disinfected using swab with alcohol each time. Sampling was performed before treatment, and 5, 10, 15, 25 and 30 hours after the treatment respectively. On the blood samples, WBC count, RBC count, hematocrit, platelet count, lymphocyte count, neutrophil count, and monocyte count were determined using hemocytometer (Nihon Kohden Corporation; MEK-6318).

6) Determination of anti-tumor effect from the measurement of tumor volume

The animals were divided into two groups: transplantation-Heat group (T-H), for which SCC-VII tumor cells ($5 \times 10^5$ cells/0.05 ml) were transplanted at first and thermal treatment at 39.0°C or 41.0°C was performed for 60 minutes 12 hours after the transplantation, and Heat-transplantation group (H-T), for which thermal treatment at 39.0°C or 41.0°C was performed at first, and 12 hours after, SCC-VII tumor cells ($5 \times 10^5$ cells/0.05 ml) were transplanted. From immediately after the first treatment, longer diameter and short diameter of the tumor were measured using esthesiometer. Tumor volume was obtained from the formula of $n \times \frac{a \times b^2}{6}$ (were $a$ is longer diameter of tumor, and $b$ is shorter diameter of tumor). The tumor volume after the first treatment was defined as 1, and relative tumor volume over time was obtained. From the number of days elapsed until the time when tumor grew twice or four times as much as the initial volume, anti-tumor effect was determined.

7) Measurement of NK cell activity

For the T-H group (for which SCC-VII tumor cells were transplanted ($5 \times 10^5$ cells/0.05 ml) and thermal treatment at 41.0°C for 60 minutes was performed 12 hours after the transplantation) and the H-T group (for which thermal treatment at 41.0°C was performed for 60 hours, and SCC-VII tumor cells ($5 \times 10^5$ cells/0.05 ml) were transplanted 12 hours after the thermal treatment), NK cell activity was determined using Cr$^{51}$-labeled YAC-1 cells. Twelve hours after the final treatment, animals were sacrificed by dislocation of cervical vertebrae. Under sterilized condition, spleen was extracted. A 100-mesh stainless steel screen was placed in a Petri dish of 5 cm in diameter containing 5 ml of sterile PBS, and the finely cut spleen was placed on the mesh. This was gently ground using a rubber portion at the tip of 5-ml syringe inner tube. Then, red blood cells were lysed in sterile red blood cell lysing solution. The remaining solution containing WBC was sampled, and after staining with Trypan blue, blood cells were counted using blood cell counter. Next, YAC-1 cells under exponential growth were separated by pipetting from the culture Petri dish using 0.025% sterile Trypsin solution. After washing this with PBS buffer solution twice, Cr$^{51}$ (500 $\mu$Ci) was added together with culture solution and this was incubated for 2 hours, and YAC-1 cells were labeled with Cr$^{51}$. Blood cells separated from spleen were added to a 96-well plate together with culture solution (5000 cells/100 $\mu$l; 10000 cells/100 $\mu$l). Then, YAC-1 cells labeled with Cr$^{51}$ at various concentrations (2000 cells, 4000 cells, 8000 cells, 16000 cells, 32000 cells/100 $\mu$l) were added together with 100-$\mu$l culture solution, and this was incubated at 37°C for 3 hours. After incubation, the 96-well plate was centrifuged at 1250 rpm for 5 minutes. Supernatant solution of the 96-well plate was placed into a 100-$\mu$l test tube, and Cr$^{51}$ was determined using Autowell scintillation counter. When NK activity is high, NK cells attack and destroy YAC-1 cells. Then, Cr$^{51}$, incorporated in YAC-1 cells is released into the culture solution, and the blood cell count increases.
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From the graph of YAC-1 cell concentration and count of the supernatant, the gradient was obtained. The ratio of activity to the control group was calculated, and NK cell activity was evaluated.

8) **Statistical analysis**

Value are expressed as the mean ± standard error (SE). The mean in each group was analyzed using ANOVA software. When there was a difference, significance was tested using Student’s t-test. P < 0.05 was regarded as significant.

**Experimental Results**

1) Changes of blood cell count after thermal treatment at 39.0°C or 40.0°C for 60 minutes respectively, WBC count, RBC count, hematocrit, platelet count, neutrophil count, monocyte count, and lymphocyte count were determined over time before treatment and 5, 10, 15, 25, and 30 hours after treatment using hemocyteter (Nihon Koden Corporation; MEK-6318). As a result, transient increase was observed in WBC count, monocyte count, and lymphocyte count after thermal treatment (Figs. 1-1, 1-2, 1-3, and 1-4). The change of WBC count reached the highest peak 15 hours after the highest peak 15 hours after the treatment at 39.0°C and 40.0°C. Then, the value returned to the initial level 30 hours later (Fig. 1-1). Neutrophils increased in 10-15 hours when treated at 39.0°C, and in 5-10 hours when treated at 40.0°C. Then neutrophils decreased and returned to the initial value 20 hours after (Fig. 1-2). The change of monocyte count showed the highest peak 15 hours after the treatment in both groups treated at 39.0°C and 40.0°C. In the group treated at 39.0°C, in the group treated at 40.0°C, it did not return to the initial value even 50 hours after the treatment, showing high value (Fig. 1-3). The change of lymphocyte count reached the highest peak 10 hours after the treatment in both groups (treated at 39.0°C and 40.0°C). The 40.0°C treatment group showed the peak again 25 hours after, and both groups returned to the initial

![Fig. 1-1. Figure shows the WBC changes after treatment. White circles (○) indicate the untreated control group. Dot circles (●) indicate heated group at 39.0 degrees for 60 minutes. The black circles (●) indicate the heated group at 40.0 degrees for 60 minutes. WBC reached peak after treatment (Heat at 39°C, 40°C) in 15 hours and it was returned to previous levels after 30 hours.](image1)

![Fig. 1-2. Figure shows the GR changes after treatment. White circles (○) indicate the untreated control group. Dot circles (●) indicate heated group at 39.0 degrees for 60 minutes. The black circles (●) indicate the heated group at 40.0 degrees for 60 minutes. GR reached peak after treatment (Heat at 39°C, 40°C) in 10 to 15 hours and it was returned to previous levels after 20 hours.](image2)
value 30 hours after (Fig. 1-4). However, no change was observed on RBC count, hematocrit and platelet count compared with the values before the treatment. In all cases, the control group without treatment exhibited a change rate of about 7% in these blood cell counts, but no significant change was found (Figs. 1-1, 1-2, 1-3, and 1-4). The increase of WBC count, monocyte count and lymphocyte count after mild hyperthermia (Figs. 1-1, 1-3, and 1-4) were observed, and the increase of neutrophils to induce inflammatory sever, which triggers the increase of immunological activity, and further, increase and decrease with time difference due to the treatment at 39.0°C and 40.0°C (Fig. 1-2) were found. All of these suggest correlation between quantity of heat and neutrophil count.

2) NK activity caused by hyperthermia before and after tumor transplantation. From animals transplanted with tumor after thermal treatment (H-T group; Heat-12hr-Transplant), and from the group treated with thermal treatment after tumor transplantation (T-H group; Transplant-12hr-Heat), spleen was extracted 12 hours after the final treatment, and activity of NK cells contained in WBC determined by Cr51 labeling method. When the control group was regarded as 1.00, it was 1.50 in H-T group, and 1.75 in T-H group.
group. Error by t test was \( \pm 12\% \) in control group, \( \pm 22\% \) in H-T group, and \( \pm 25\% \) in T-H group, showing significant difference in NK cell activity between the two groups (Fig. 2). The increase of NK cell activity due to mild hyperthermia suggests the activation of the entire immunological response, and we can expect much on anti-tumor effect of this therapy.

3) Anti-tumor effect by hyperthermia before and after tumor transplantation

When the number of days required until the time when the tumor grew 4 times in size was evaluated from tumor growth curve (Fig. 3) in T-H group (treated with hyperthermia after tumor transplantation), H-T group (transplanted with tumor after hyperthermia), and the control group without treatment. The results were 3.6 days in H-T group. When the control was regarded as 1.00, it was 1.22 in T-H group, and 1.58 in H-T group, and this confirms that tumor growth is delayed when tumor is transplanted after hyperthermia treatment. The findings of growth inhibition in the tumor transplanted after hyperthermia suggest that it was induced by the increase of WBC count, monocyte count, and lymphocyte count and by the activation of NK cells. By treating with mild hyperthermia before extraction of tumor, activation of NK cells can be expected, and this suggests the improvement of the course after the therapy.

4) Anti-tumor effect by thermal treatment every day and every other day

The number of days required until the time when the tumor grew 4 times in size was evaluated from tumor growth curve (Fig. 4) in three groups: ED-H group (heating every day) (the group treated with mild hyperthermia at 41°C for 30 minutes every day after transplantation of SCC-VII tumor cells (\( 5 \times 10^5 \) cells/0.05 ml)), EOD-H group (heating every other day) (the group treated with thermal treatment every other day), and in the control group without treatment. The results were 3.5 days in the control group, 4.3 days in EOD-H group, and 5.6 days in
ED-H group. When the control was regarded as 1.00, it was 1.22 in EOD-H group, and 1.60 in ED-H group. This reveals that anti-tumor effect can be obtained with mild hypertermia at 41°C for 30 minutes and that the effect is higher when treated every day, and there is not much influence on the resistance to heat. In general, hyperthermia is conducted 2-3 times per week because of the resistance to heat, but the results of the present study suggest that there is no need to take special care about the resistance to heat.

Discussion

When cancer cells proliferate, oxygen, nutrition and productive components must be supplied to the cells from the host just as in the case of normal cells, and it is believed that cancer secretes various types of inductive factors and growth factor to adjust the conditions for division and growth in human body. In order that cancer cells avoid the attack from the immunocompetent cells and continue to grow, cancer cells must behave just as normal cells and receive the supply of oxygen and the like from the host. For this purpose, cancer cells induce and form new capillary blood vessels from the neighboring blood vessels of the host and creates advantageous conditions in human body. There have been a number of reports describing the growth of cancer in new blood vessels in ischemic state due to the presence of tumor or describing the presence of vascular growth factors such as VEGF (vascular endothelial growth factor) in tumor vascular growth. On the growth of normal blood vessel, Clark asserts that blood vessel with high blood flow develops further, while blood vessel with low blood flow or blood stagnation retracts. Also, blood vessel with abundant blood flow grows in the growth of tumor blood vessel, while blood vessel retracts and disappears when blood flow is low or is stopped, and this is demonstrated from ecological observation. Chemotherapy basically adversely affects cell division, and this is based on the assumption that cancer cells have shorter cell cycle and more active cell division than somatic cells. Therefore, the longer the period of chemotherapy is, the more the damage on normal cells increases, and adverse effect is an important problem. Radiotherapy and hyperthermia have the same effects as the case of carcinostatic agent as described above so far as direct purpose of the therapy is necrosis of cancer cells and inhibition of growth. From the view point of the risk of side effect, hyperthermia is safer, and mild hyperthermia is much safer. In recent years of biological response modifier (BRM), which adjusts and activates immunological conditions in human body. These include the agents, which activate and adjust immunocompetent cells to a part or the entire process of carcinogenesis and cancer growth or cytokines, and much expectation is now placed on the results of further clinical studies in future. In the dynamics of tumor blood vessel in hyperthermia, there are factors such as blood flow increase of normal cells, blood flow stagnation at central part of the tumor, poor supply of oxygen and nutrition from these reasons, and decrease of pH value. These are similar to the mechanisms of growth such as retraction and disappearance in homodynamic of new blood vessel of tumor, and this seems to be related to the network of cytokines used as VEGF or heat inductive substance, which regulates these mechanisms. There are not many references in the literature on the immunological activity caused by mild hyperthermia. In the present article, the increase of immunological activity is confirmed to explain the mechanism to provide anti-tumor effects at relatively mild temperature.

From the results of the present study, it is confirmed that neutrophil count, WBC count, monocyte count and lymphocyte count increase and NK cells are activated before the other cells when treatment is
performed with mild hyperthermia at mild temperature of 42.5°C or lower. Further, when tumor was transplanted after the treatment by hyperthermia, the delay of tumor growth was observed. Also, mild anti-tumor effect was confirmed after treatment with hyperthermia at 39°C. These results agree well with typical activation model of series of immunocompetent cells, and this suggests the possibility of regulation of immunological potency by quantitative thermal treatment. If we set up a hypothesis from these results, anti-tumor effect is not direct physical damage caused by mild hyperthermia, but it efficiently induces a series of immunological responses such as the increase of neutrophil count, monocyte count and lymphocyte count in the dynamics of tumor blood cells due to heating, and activation of NK cells. Further, more precisely, the increase is observed in neutrophil count, monocyte count and lymphocyte count due to development of pseudo-inflammation caused by thermal treatment. To prove this hypothesis, it appears to be necessary to perform further study in future, i.e. to study at least the quantitative correlation between the increase of neutrophils and the quantity of heat added, to evaluate the activation of macrophages associated with it, to watch the tendencies of IL-2 and IL-3, to determine the details such as activity of CD4, CD8, etc. As described above, H-T group, while T-H group was higher in NK cell activity. This may be attributed to the fact that a series of immunocompetent cells responded after hyperthermia treatment (a peak was reached 5-15 hours after the treatment by hyperthermia in the present study). As a result, the activity of NK cells may have reached the highest value (12 hours after the treatment). In H-T group, 24 hours were required until the termination of response of a series of immunocompetent cells (after 9-19 hours) and until the determination of NK activity (24 hours). For this reason, the timing after the termination of immunological response is beyond the peak of NK activity. Also, the site treated with hyperthermia was the site of the tumor transplanted subcutaneously in hemopoietic organs in bone marrow of femoral region. Further, this may have induced the increase of WBC, neutrophil, monocyte and lymphocyte and activation of NK cells. If it is supposed that quantitative stimulation of femoral region by mild hyperthermia has induced the activation of hemopoietic organs in bone marrow of femoral region and this has activated immunological potency, mild hyperthermia seems to be a useful and effective auxiliary therapy which is not only effective for the treatment of malignant tumor but also for the treatment of diseases related to immunological potency (e.g. viral hepatitis type C, collagen diseases, AIDS, postoperative physical restoration, auxiliary therapy during thermotherapy, elimination of immunodeficiency, etc.). Also, it was observed that the treatment everyday by mild hyperthermia has higher anti-tumor effect than the treatment given every other day. This suggests that the effects with higher efficiency can be expected by the heating procedure (total physical quantity of heat and timing of treatment). Hasegawa et al. reported that thermal effects could be reinforced if heated quickly even when the temperature and the time for treatment were the same. Imada et al. paid attention on QOL of the patients and reported that if the patient was in prone position during hyperthermia, heat feeling and pain were alleviated, and higher input could be applied. Further, Imada et al. described that higher efficiency could be achieved by overheating with high frequency of high output. Based on the reinforcement of immunological activity by mild hyperthermia as reported in the present study by application of various types of mild hyperthermia, this appears to be an effective therapeutic method, in which emphasis is put on QOL of the patients with severe diseases or elderly patients, to whom normal
thermotherapy cannot be indicated\(^31\). If would be possible to apply the treatment quantitatively, it would contribute to immunological activity, and the scope of the therapy may be expanded to the preventive treatment. Further, the activation of immunological potency as discussed in this article would contribute to the improvement of postoperative prognosis of cancer treatment such as postoperative prognosis of the patients. It would also be much helpful to the inhibition of metastatic tumor.

**Conclusion**

The results of the present study confirmed: (1) Anti-tumor effect can be given by thermal treatment at relatively mild temperature (mild hyperthermia at 39°C-41°C); (2) The increase of neutrophils is dependent on the quantity of heat added; (3) immunological response of monocytes and lymphocytes are associated with it; (4) Activity of the immunological potency as a whole such as activation of NK cells was also confirmed.

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マイルド・ハイパーサーミアによる免疫能活性と抗腫瘍効果

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要旨：温熱治療は一般的に 42.5℃以上の温度で行われている。しかし、我々は 42.5℃以下の温度による温熱治療によっても、免疫能活性が発生し、その結果、抗腫瘍効果の発生する事を見た。実験には SCC-VII 腫瘍を大腿部皮下に担癌させた C3H マウスを用いた。担癌マウスの大腿部に対して 39℃から 41℃の低温で温熱治療を恒温水槽によって 1 時間加えた。温熱処理前後の白血球数、リンパ球数、NK 細胞活性を調べた。42.5℃以下のマイルド温熱処理によって抗腫瘍効果が観察され、その腫瘍成長遅延に伴って白血球数、リンパ球数の一過性増加と NK 細胞活性が観察された。これらの結果はマイルド・ハイパーサーミアによって、免疫能が活性化することを示唆している。おそらく、大腿部をマイルド・ハイパーサーミアで定量的に刺激して、大腿部骨髄の造血器官が活性化し、免疫能が活性化するのであれば、マイルド・ハイパーサーミアは癌治療患者に対しては癌の転移を抑える可能性があり、更に免疫能が関与する疾患の治療（例えば C 型肝炎、膠原病、エイズ、術後の回復、温熱治療時の補助治療、その他免疫不全の解消等）に有効な治療となると考えられる。