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Guest Editorial

Hyperthermia and Cancer Therapy

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Since the thermal sensitivity of cancer cells is, as a rule, only slightly higher than that of normal cells [1, 15, 16, 17, 19, 25], hyperthermia, when applied alone, merely shows low therapeutic selectivity. To make hyperthermia more effective it has been attempted to focus power input directly to the tumor via radiofrequency [1, 18, 22] or ultrasound [24]. Moreover, a higher selectivity was expected with a combination of focused ionizing radiation and hyperthermia [20, 21, 27, 29]. All these methods failed to solve the main problem in any cancer therapy, namely, the destruction of metastases.

Since 1965 we have been working with stimulation of glycolysis of cancer cells, and consequently with their specific hyperacidification, to establish a generally utilizable and selective therapeutic element directed towards primary tumors, as well as micrometastases [1]. The selective lowering of pH to 6.0 in the interstitium of tumor tissues and to approximately 6.7 in the venous parts of cancer tissue capillaries is attained by a three- to fivefold elevation of blood-glucose levels for several hours [7, 14]. This clinical method is fully matured now [23]. We discovered in 1968 [1] that hyperthermia and acidification act synergistically, and this was confirmed by others [26]. For this reason, hyperthermia should be therapeutically applied only in combination with optimal tumor hyperacidification [11]. Recent investigations on the selective inhibition of microcirculation in tumor tissues [6, 10, 28] disclosed that the tumor tissue vasculature is a more sensitive target for hyperthermia combined with overacidification than the tumor cells themselves [10]. This was experimentally confirmed [14] and has decisive consequences: (1) Hypoxia in tumor cells is markedly enhanced and, hence, their thermal sensitivity is increased; and (2) the convection cooling of tumors by the bloodstream is practically abolished. There is a selective temperature increase in the tumor, compared to the surrounding normal tissue.

Under favorable conditions the inhibition of microcirculation can force a total irreversible occlusion of the cancer tissue vasculature by combined hyperthermia and hyperacidification [5]. With this process, the regressing tumor is widely separated from circulation and the outflow of toxic products is inhibited. The temperatures necessary for tumor destruction are in the order of 42–42.5° C (also in the adjacent host tissue) for 60–240 min. The physical problem consists of maintaining temperatures like these in any tumor tissue regardless of its localization (deep-seated tumors!) and to avoid impairment of normal tissues.

Heat-theory evaluations considering blood flow parameters and heat dissipation by convection and conduction provide the temperature distribution in the section to be heated [8, 13] and demonstrate that the common decimeter and radio frequency (rf) equipment is not sufficient for that purpose. On the contrary, the CMT Selectotherm procedure is at present the chosen method [3, 12]. A specially constructed rf applicator moves parallel to the body's surface and scans an area of, e.g., 45×45 cm^2. This scanning principle combined with intensive external skin cooling maintains the temperature differences between host tissue and maximally heated tissue layers in the range of $< 2°$ C, regardless of the localization of the tumor, provided that the method of two-step hyperthermia already proposed in 1965 [1] is applied: On the total body hyperthermia of 40° C (first step) the local rf hyperthermia (second step) is superimposed. Using plausible assumptions, calculations on this two-step hyperthermia revealed that at 40° C core temperature the local temperature will decline from the maximum at 42.5° C (2.75 cm beneath the cooled skin) to only 42° C at 10 cm depth, whereas the temperature falls to 40° C if hyperthermia is performed as single-step procedure without initial basic hyperthermia. The great advantage of the two-step technique is that both the absolute temperature increase needed and the in-depth temperature gradient are conspicuously lower during the local hyperthermic phase. By this means the risk of thermal impairment of normal tissues near to the skin is decisively

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reduced. According to the Cancer Multistep Therapy (CMT) concept [4, 6], total body hyperthermia (40° C) is generated without any technical effort as spontaneous hyperthermia [2] as a result of stimulated glucose and oxygen metabolism. The latter additionally stabilizes the circulation. Because of the two-step method and the scanning principle, local hyperthermic treatment can be extended successively to different body sections, which are locally heated to 42.0–42.5° C, while the total body temperature does not exceed 40° C. The stepwise shift of the rf applicator and the variable scanning parameters permit the attack on metastases via high-dosage hyperthermia in the entire body without any critical circulatory risk to the patient.

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References

1. Ardenne M von (1970/71) Theoretische und experimentelle Grundlagen der Krebs-Mehrschritt-Therapie, vol 1 and 2, 2nd edn. VEB Verlag Volk und Gesundheit, Berlin
2. Ardenne M von (1976) Vereinfachung der Krebs-Mehrschritt-Therapie durch induzierte Spontanhyperthermie. Krebsgeschehen 8:26
3. Ardenne M von (1978) On a new physical principle for selective local hyperthermy of tumor tissues. In: Streffer C (ed) Cancer therapy by hyperthermia and radiation. Urban Schwarzenberg, Baltimore München, p 96
4. Ardenne M von (1978) Prinzipien und Konzept 1977 der Krebs-Mehrschritt-Therapie. Arch Geschwulstforsch 48:504
5. Ardenne M von (1978) Selektive Verschließung der Krebsgewebekapillaren durch einen Hyperthermiestoß während Hyperglykämie. Dtsch Gesundheitswes 33:2158
6. Ardenne M von (1979) Über den Entwicklungsstand der Krebs-Mehrschritt-Therapie. Selektiver Stop der Mikrozirkulation in den Krebsgeweben durch ihre optimierte Übersäuerung + Hyperthermiestoß nach dem Selectotherm-Verfahren. Med Uns Zeit 3:34
7. Ardenne M von, Ardenne A von (1977) Berechnung des pH-Profils im Interkapillarraum der Krebsgewebe für die Fälle mit und ohne Langzeit-Glukose-Infusion. Schlußfolgerungen für die Gestaltung der Therapie des Krebses. Res Exp Med 171:177
8. Ardenne M von, Kell E (1979) Berechnung des dynamischen Aufheizprozesses in mehrschichtigen Modellgeweben bei Lokalhyperthermie nach dem CMT-Selectotherm-Verfahren. Arch Geschwulstforsch 49:590
9. Ardenne M von, Reitnauer PG (1979) Verstärkung der mit Glukoseinfusion erzielbaren Tumorübersäuerung in vivo durch lokale Hyperthermie. Res Exp Med 175:7
10. Ardenne M von, Reitnauer PG (1980) Selective occlusion of cancer tissue capillaries as central mechanism of the cancer multistep therapy. Jpn J Clin Oncol (in press)
11. Ardenne M von, Krüger W (1980) The use of hyperthermia within the frame of cancer multistep therapy. Ann NY Acad Sci (in press)
12. Ardenne M von, Böhme G, Kell E (1979) On the optimization of local hyperthermy in tumors based on a new radiofrequency procedure. Local hyperthermy of large body areas using the CMT Selectotherm method. J Cancer Res Clin Oncol 94:163
13. Ardenne M von, Böhme G, Kell E, Reitnauer PG (1979) Die Bedeutung der Wärmeleitung für die therapeutischen Grenzen der selektiven Lokalhyperthermie von Krebsgeweben. Radiobiol Radiother 20:529
14. Ardenne M von, Lippmann HG, Reitnauer PG, Justus J (1979) Histological proof for selective stop of microcirculation in tumor tissue at pH 6.1 and 41° C. Naturwissenschaften 66:59
15. Bender E, Schramm T (1966) Untersuchungen zur Thermosensibilität von Tumor- und Normalzellen in vitro. Acta Biol Med Germ 17:515
16. Cavaliere R, Ciocatto EC, Giovanella BC, Heidelberger Ch, Johnson RO, Margottini M, Mondovi B, Moricca G, Rossi-Fanelli A (1967) Selective heat sensivity of cancer cells. Cancer 20:1351
17. Dickson JA (1977) The effects of hyperthermia in animal tumor systems: Recent results. Cancer Res 59:43
18. Guy AW, Lehmann JF, Stonebridge JB (1974) Therapeutic applications of electromagnetic power. Proc. IEEE 62:55
19. Henle KJ, Dethlefsen LA (1978) Heat fractionation and thermotolerance: A review. Cancer Res 38:1843
20. Hill SA, Fowler JF (1978) Combined effect of heat and X-rays on two types of mouse tumor. In: Streffer C (ed) Cancer therapy by hyperthermia and radiation. Urban Schwarzenberg, Baltimore Munich, p 251
21. Johnson RJR (1978) Radiation and hyperthermia. In: Streffer C (ed) Cancer therapy by hyperthermia and radiation. Urban Schwarzenberg, Baltimore München, p 89
22. LeVeen HH, Wapnik S, Piccone V, Falk G, Ahmed N (1976) Tumor eradication by radiofrequency therapy. JAMA 235:2197
23. Lippmann HG, Graichen D (1977) Glukose- und K^+-Bilanz während hochdosierter intravenöser Glukosezufuhr. Infusionstherapie 4:166
24. Marmor J, Nager C, Hahn GM (1977) Tumor regression and immune recognition after localized ultrasound heating. Radiat Res 70:633
25. Milder JW (ed) (1979) Conference on hyperthermia an cancer treatment. Cancer Res 39:6, Part 2, p 2235
26. Overgaard J (1976) Influence of extracellular pH on the viability and morphology of tumor cell growth to hyperthermia. Cancer Res 56:1243
27. Robinson JE, Wizenberg MJ (1974) Thermal sensitivity and the effect of elevated temperature on the radiation sensitivity of Chinese hamster cells. Acta Radiol 13:241
28. Song CW (1978) Effect of hyperthermia on vascular functions of normal tissues and experimental tumors. J Natl Cancer Inst 60:711
29. Suit HD, Gerweck LE (1979) Potential for hyperthermia and radiation therapy. Cancer Res 39:2290

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