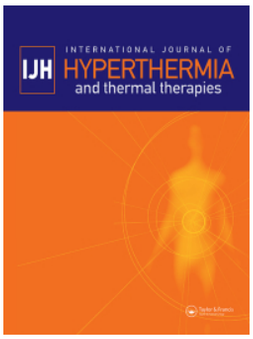

International Journal of Hyperthermia

ISSN: 0265-6736 (Print) 1464-5157 (Online) Journal homepage: informahealthcare.com/journals/ihyt20

Tissue physiology and the response to heat

Michael R. Horsman

To cite this article: Michael R. Horsman (2006) Tissue physiology and the response to heat, International Journal of Hyperthermia, 22:3, 197-203, DOI: 10.1080/02656730600689066

To link to this article: https://doi.org/10.1080/02656730600689066

Int. J. Hyperthermia, May 2006; 22(3): 197–203

Taylor & Francis
Taylor & Francis Group

Tissue physiology and the response to heat

MICHAEL R. HORSMAN

Department of Experimental Clinical Oncology, Aarhus University Hospital, Aarhus C, Denmark

(Received 28 October 2005; revised 26 February 2006; accepted 13 March 2006)

Abstract

The most important physiological parameter influencing tissue response to heat is blood flow. At mild hyperthermia temperatures blood perfusion increases in many tumours and this effect is heating time-, temperature- and tumour-dependent. These flow increases can improve tumour oxygenation.

When heating is terminated, perfusion and oxygenation commonly recover, although how quickly this occurs appears to be tumour-specific. While these effects are unlikely to have any anti-tumour activity they can be exploited to improve the combination of heat with other therapies. However, since similar physiological effects should occur in normal tissues, such combination therapies must be carefully applied. Heating tumours to higher temperatures typically causes a transient increase in perfusion during heating, followed by vascular collapse which if sufficient will increase tumour necrosis. The speed and degree of vascular collapse is dependent on heating time, temperature and tumour model used.

Such vascular collapse generally occurs at temperatures that cause a substantial blood flow increase in certain normal tissues, thus preferential anti-tumour effects can be achieved. The tumour vascular supply can also be exploited to improve the response to heat. Decreasing blood flow, using transient physiological modifiers or longer acting vascular disrupting agents prior to the initiation of heating, can both increase the accumulation of physical heat in the tumour, as well as increase heat sensitivity by changing the tumour micro-environmental parameters, primarily an increase in tumour acidity.

Such changes are generally not seen in normal tissues, thus resulting in a therapeutic benefit.

Keywords: *Hyperthermia, physiological effects, blood flow, physiological modifiers, vascular disrupting agents*

Introduction

There is a strong relationship between tissue physiology and the response of that tissue to heating. The most important physiological parameter in this context is blood flow. When any tissue is heated various physiological changes occur, the majority of which are secondary

Correspondence: Michael R. Horsman, PhD, DMSc, Department of Experimental Clinical Oncology, Aarhus University Hospital, Nørrebrogade 44, Building 5, DK-8000 Aarhus C, Denmark. Tel: +45 89 49 26 22. Fax: +45 86 19 71 09. E-mail: mike@oncology.dk

ISSN 0265–6736 print/ISSN 1464–5157 online
DOI: 10.1080/02656730600689066

to changes in blood flow [1]. Blood flow is also one of the major vehicles by which heat is dissipated from tissues, thus the tissue blood supply will have a significant influence on the ability to heat that tissue [2]. In general, the lower the rate of blood flow then the easier it is to heat. Blood flow is also important in determining the micro-environmental conditions found within tissues, especially in tumours [3, 4]. Although solid tumours can have blood flow values that can be greater than that of certain normal tissues, when compared to normal tissues the tumour blood supply is generally primitive and chaotic in nature, which can result in areas that are nutrient-deprived, low in oxygen and highly acidic and cells that exist in these adverse conditions are generally more sensitive to the cytotoxic effect of heat. The aim of this presentation will be to briefly review the physiological changes that occur in following heating and how the physiology can be exploited to improve the response to hyperthermia.

Physiological consequences of heating

The physiological changes that occur when tumours are heated at different temperatures is illustrated in Figure 1. Mild heat temperatures cause an increase in blood flow. At the same time there is a corresponding increase in the oxyhaemoglobin saturation of the individual red blood cells within tumour micro-vessels. These changes will lead to an overall increase in oxygen availability. Other studies have also shown that mild hyperthermia temperatures improve tumour oxygenation status [5, 6]. At higher temperatures one may see a very transient increase in blood flow during the heating period, but vascular damage soon begins to occur and this will rapidly lead to a decrease in tumour blood flow [2, 7, 8]. With higher heat temperatures there is also a corresponding decrease in oxyhaemoglobin saturation, and these changes will result in a decrease in overall oxygen availability. This lack of oxygen will also give rise to a decrease in tumour pH and ultimately lead to ischemia and cell death [3]. The degree of vascular shut-down at the higher temperatures appears to be dependent on the

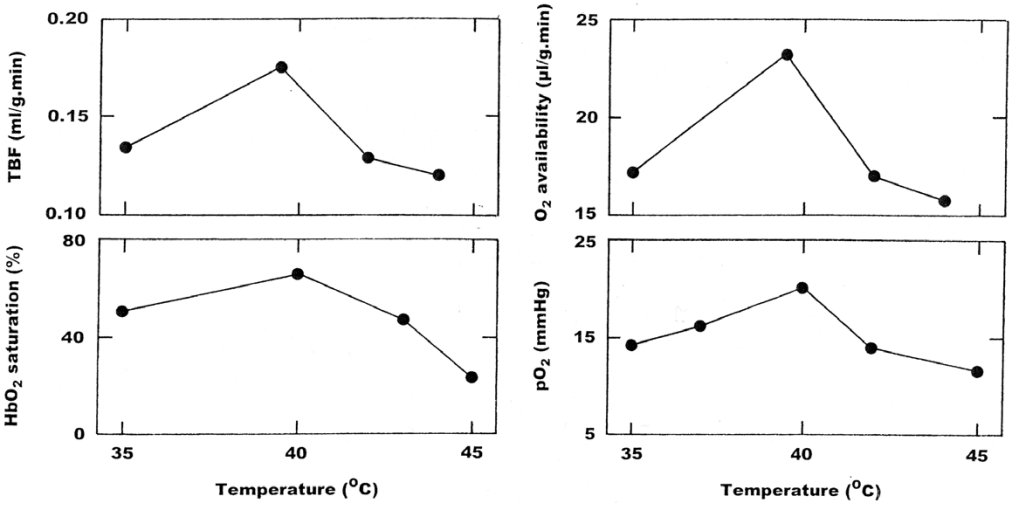

Figure 1. Physiological changes induced during heating of tissue-isolated tumour preparations as a function of tumour temperature. Results show tumour blood flow (TBF), haemoglobin-oxygen (HbO_2) saturation in tumour micro-vessels, tumour oxygen availability and mean intra-tumour oxygen partial pressure (pO_2). (Adapted from [1].)

time and temperature of heating. It is also dependent on the tumour type, and this may be a reflection of the tumour blood flow prior to treatment, since it has been shown that the lower the pre-treatment flow then the more severe the heat induced shut-down [9]. Normal tissues typically show a very different vascular response to heat, with flow essentially increasing as the temperature increases, even at temperatures that produce substantial vascular occlusion in tumours [7, 9].

Probably the most controversial aspect of the physiological effects of hyperthermia is how long the improvements in tumour oxygen at mild hyperthermia treatments actually last. In a C3H mouse mammary carcinoma, tumour oxygenation returned to normal within a matter of minutes after the heating was stopped [6]. Others have shown that the enhanced oxygenation can actually last for up to 24-h after heating [5], although this effect is difficult to explain because the physiological changes that account for the enhanced tumour oxygenation at these temperatures are unlikely to be prolonged. There is even clinical data that seems to support the argument for a prolonged improvement in oxygenation at mild temperatures [10, 11]. However, those clinical studies also showed that this increased oxygenation correlated with the degree of damage seen, and an additional pre-clinical study clearly demonstrated enhanced oxygenation 24–48 h after heating at temperatures and treatment times that were severe and caused substantial tumour control, presumably due to vascular shut-down that would have been expected with such treatments [12]. This may suggest that the apparent improvements in oxygenation in the clinical studies may simply be reflecting damage resulting from the higher temperatures and not 'reoxygenation' at lower temperatures.

Exploiting tumour physiology to improve heating

Since blood flow to tissues influences both the ability to heat the tissue and the damage induced by heat, it naturally follows that modifying blood flow should be a biologically valid approach for improving hyperthermia. Numerous studies have now shown that decreasing tumour blood flow either by physical clamping [13–15] or physiological modification using high-dose hydralazine [16–20], sodium nitroprusside [21–23] or glucose [24–27] are effective at improving tumour response to hyperthermia. This is illustrated in Figure 2 for hydralazine (HDZ), in which heating tumours at the time of maximal vascular shut down by HDZ increases the slope of the heat dose-response curve and that this occurs at all temperatures from 40.5–43.5°C. Similar effects are unlikely to occur in normal tissues, primarily because such physiological modifiers do not induce significant reductions in normal tissue blood flow [30]. However, despite the therapeutic benefit of these approaches, the clinical applicability of such methods remains questionable.

A more clinically relevant approach may be the use of vascular disrupting agents (VDAs). These damage tumour vasculature and thus reduce blood flow, without producing similar effects in normal tissues [28, 31–35], and several VDAs are currently in clinical testing [36]. Many of these VDAs have also been combined with hyperthermia, including tumour necrosis factor [37, 38], arsenic trioxide [39, 40], vinblastine [41], flavone acetic acid [28, 29], 5,6-dimethylxanthenone-4-acetic acid [42] and combretastatin A-4 disodium phosphate [43–45] and in every case there was an enhancement of the heat response. This effect was time- and schedule-dependent, with the maximum response generally observed if the heating was started 1–6 h after VDA injection [28, 29, 39, 40, 42–46] and this clearly corresponded to the time of maximal reduction in tumour blood flow in those studies. Injecting VDAs after heating has been shown to be substantially less effective at enhancing

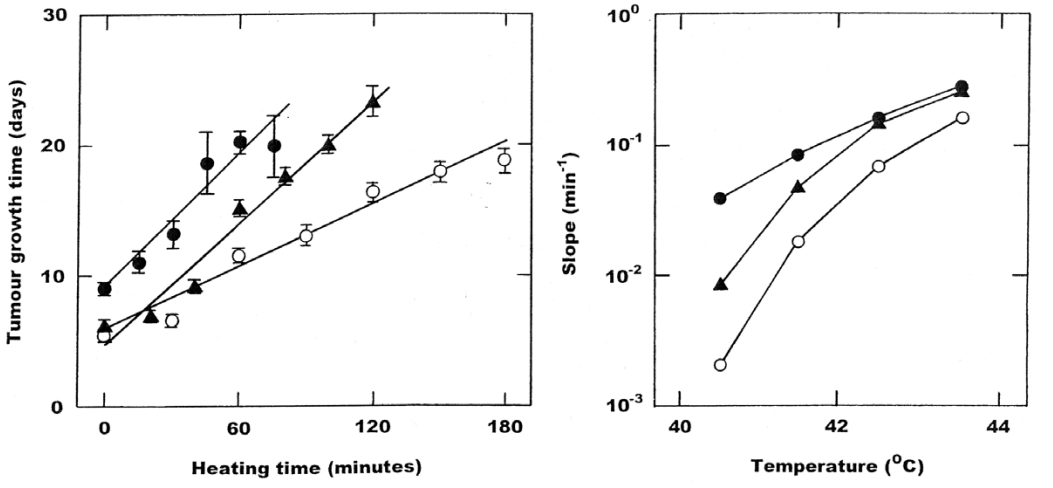

Figure 2. The effect of blood flow modifiers on the response of a C3H mammary carcinoma to heat. Tumours were locally heated at 42.5°C + drugs for up to 180 min and the tumour growth time (time taken for tumours to grow from 200–1000 mm^3) calculated (left panel), with the results shown as means (+1 SE) for an average of 12 animals per group. The slope values for these curves and for similar data at other temperatures were then calculated and are shown (right panel). For both figures the results are for heat alone (○) or heating started 30 min after injecting HDZ (▲; 5 mg kg^{-1}; i.v.) or 3 h after FAA (●; 150 mg kg^{-1}; i.p.). (Adapted from [17, 28, 29] and unpublished data.)

the heat response [28, 42, 45, 46] and in most cases did not appear to be greater than a simple additive effect of the VDA and heat alone. Typical results illustrating the enhancement of heat damage by VDAs are shown in Figure 2 using flavone acetic acid (FAA) as the example. As with most VDAs, FAA alone had a small effect on tumour growth, but when tumours were heated at the time of maximal vascular shut down there was a significant increase in the heat dose-response curve. Similar to HDZ, the FAA induced enhancement of heat damage is temperature dependent (Figure 2). However, although the enhancement by FAA at higher temperatures resembled the effect seen with HDZ, at mild hyperthermia treatments the effect is much larger. Similar enhancements have been seen with other VDAs [42, 45]. Why this should be is not entirely clear. The reductions in tumour blood flow induced by HDZ and VDAs can lead to a better tumour heating [17, 19, 20, 41, 46]. However, as a result of the vascular shut down there is a corresponding decrease in tumour pH with both HDZ and VDAs [46, 47, Horsman and Maxwell unpublished observations] and since it is well known that cells under low pH are more sensitive to killing by heat [48, 49], part of the enhanced heat response is related to an increase in tumour damage [17, 18, 20, 28, 29, 42, 45] and this latter effect may play the more significant role. However, some studies revealed that heat damage could be maximally enhanced in situations where the effects on tumour perfusion were well below maximal [41, 45]. This suggests that unlike the situation with physiological modifiers of tumour blood flow, the enhancement of heat damage by VDAs involves other, as yet unknown, factors unrelated to a simple reduction in tumour blood flow, and it may be these factors which account for the differences at mild temperatures.

Some studies have investigated the possible enhancement of heat damage by VDAs in normal tissues. In general, VDAs do enhance heat response in such tissues [28, 42–45].

However, these increases have always been far less than those seen in tumours, thus resulting in a therapeutic benefit.

Conclusions and clinical relevance

Hyperthermia on its own had no role to play in the curative treatment of tumours in humans and its clinical potential lies in its use as an adjuvant with other more conventional treatments [50]. Indeed, several clinical studies have demonstrated the benefit of combining hyperthermia with radiation or chemotherapy [51–53]. However, the physiological changes induced by heating could be better exploited to improve this. High temperatures decrease blood flow and could be used to trap chemotherapeutic drugs in tumours. There is also a decrease in tumour pH and this is known to increase the sensitivity of certain drugs [54]. Mild hyperthermia treatments increase tumour perfusion and this could be utilised to improve drug delivery. At the same time the increase in tumour oxygenation would be expected to increase radiation sensitivity; however, this would probably require giving the heat at the same time or immediately prior to irradiating, which is not how current schedules are used.

With the blood flow modifiers, especially the VDAs, the greatest advantage lies in the fact that, when combined with mild heat treatments of ~41.5°C, they produce effects that are similar to those seen at temperatures of 42.5–43°C alone. Clinically, temperatures of ~43°C are generally considered necessary for efficacy [52], but it is often difficult to achieve this temperature and less effective mild temperatures of ~41.5°C are often seen [55]. Vascular modifiers thus appear to be an effective method for converting the mild temperatures into a more efficient therapy, which suggests that if future clinical trials with hyperthermia were to include such agents in the treatment regime, we may overcome the problem of ineffective heating of tumours and many more trials should be beneficial.

Acknowledgements

This presentation was made possible by financial support from the Danish Cancer Society and the Danish Research Agency.

References

1. Vaupel P, Kallinowski F. Physiological effects of hyperthermia. In: Streffer C, editor. Recent results in cancer research. Vol. 104. Heidelberg, Berlin: Springer-Verlag; 1987. pp 71–109.
2. Patterson J, Strang R. The role of blood flow in hyperthermia. Int J Radiat Oncol Biol Phys 1979;5:235–241.
3. Vaupel P, Kallinowski F, Okunieff P. Blood flow, oxygen and nutrient supply, and metabolic micro-environment of human tumors: A review. Cancer Res 1989;49:6449–6465.
4. Vaupel P, Kelleher DK. Metabolic status and reaction to heat of normal and tumor tissue. In: Seegenschmiedt MH, Fessenden P, Vernon CC, editors. Thermoradiotherapy and thermochemotherapy. Vol. 1. Berlin, Heidelberg, New York: Springer; 1995. pp 157–176.
5. Iwata K, Shakil A, Hur WJ, Makepeace CM, Griffin RJ, Song C. Tumour pO2 can be increased markedly by mild hyperthermia. Br J Cancer 1996;74(suppl. XXVII):S217–S221.
6. Horsman MR. Overgaard J. Can mild hyperthermia improve tumor oxygenation? Int J Hyperthermia 1997;13:141–147.
7. Song CW, Patten MS, Chelstrom LM, Rhee JG, Levitt SH. Effect of multiple heatings on blood flow in RIF-1 tumours, skin and muscle of C3H mice. Int J Hyperthermia 1987;3:535–545.

8. Gyldenhof B, Horsman MR, Overgaard J. Hyperthermia-induced changes in the vascularity and histopathology of a murine tumour and its surrounding normal tissue. In: Franconi C, Arcangeli G, Cavaliere R, editors. Hyperthermic oncology. Vol. II. Rome: Tor Vergata; 1996. pp 780–782.
9. Vaupel PW. Effects of physiological parameters on tissue response to hyperthermia: New experimental facts and their relevance to clinical problems. In: Gerner EW, Cetas TC, editors. Hyperthermia Oncology 1992. Tucson: Tucson Arizona Board of Regents; 1993. pp 17–23.
10. Brizel DM, Scully SP, Harrelson JM, Layfield LJ, Dodge RK, Charles HC, Samulski TV, Proznitz LR, Dewhirst MW. Radiation therapy and hyperthermia improve the oxygenation of human soft tissue sarcomas. Cancer Res 1996;56:5347–5350.
11. Jones EL, Prosnitz LR, Dewhirst MW, Marcom PK, Hardenbergh PH, Marks LB, Brizel DM, Vujaskovic Z. Thermochemotherapy improves oxygenation in locally advanced breast cancer. Clin Cancer Res 2004;10:4287–4293.
12. Hetzel FW, Chopp M, Dereski MO. Variations in pO_2 and pH response to hyperthermia: Dependence on transplant site and duration of treatment. Radiat Res 1992;131:152–156.
13. Thrall DE, Gillette EL, Dewey WC. Effect of heat and ionizing radiation on normal and neoplastic tissue of the C3H mouse. Radiat Res 1975;63:363–377.
14. Hill SA, Denekamp J. The effect of vascular occlusion on the thermal sensitization of a mouse tumor. Br J Radiol 1978;51:997–1002.
15. Wallen CA, Colby TV, Stewart JR. Cell kill and tumor control after heat treatment with and without vascular occlusion in RIF-1 tumors. Radiat Res 1986;106:215–223.
16. Voorhees WD, Babbs CF. Hydralazine-enhanced selective heating of transmissible venereal tumor implants in dogs. Eur J Cancer Clin Oncol 1982;19:1027–1033.
17. Horsman MR, Christensen KL, Overgaard J. Hydralazine-induced enhancement of hyperthermic damage in a C3H mammary carcinoma *in vivo*. Int J Hyperthermia 1989;5:123–136.
18. Kalmus J, Okunieff P, Vaupel P. Dose-dependent effects of hydralazine on microcirculatory function and hyperthermic response of murine FSaII tumors. Cancer Res 1990;50:15–19.
19. Dewhirst MW, Prescott DM, Clegg S, Samulski TV, Page RL, Thrall DE, Leopold K, Rosner G, Acker JC, Oleson JR. The use of hydralazine to manipulate tumour temperatures during hyperthermia. Int J Hyperthermia 1990;6:971–983.
20. Honess DJ, Hu DE, Bleehen NM. A study of the mechanism of hydralazine enhancement of thermal damage in the KHT tumour. Int J Hyperthermia 1991;7:667–679.
21. Prescott DM, Samulski TV, Dewhirst MW, Page RL, Thrall DE, Dodge RK, Oleson JR. Use of nitroprusside to increase tissue temperature during local hyperthermia in normal and tumor-bearing dogs. Int J Radiat Oncol Biol Phys 1992;23:377–385.
22. Krossnes BK, Mella O, Dahl O. Use of the vasodilator sodium nitroprusside during local hyperthermia: Effects on tumor temperature and tumor response in a rat tumor model. Int J Radiat Oncol Biol Phys 1996;36:403–415.
23. Poulson JM, Vujaskovic Z, Gaskin AA, La Rue SM, Meyer RE, Prescott DM, Samulski TV, Thrall DE, Dewhirst MW. Effect of calcitonin gene related peptide vs sodium nitroprusside to increase temperature in spontaneous canine tumours during local hyperthermia. Int J Hyperthermia 2004;20:477–489.
24. Urano M, Montoya V, Booth A. Effect of hyperglycemia on the thermal response of murine normal and tumor tissue. Cancer Res 1983;43:453–455.
25. Murray D, Milas L, Meyn RE. DNA damage produced by combined hyperglycemia and hyperthermia in two mouse fibrosarcoma tumors *in vivo*. Int J Radiat Oncol Biol Phys 1984;10:1679–1682.
26. Osinsky SP, Bubnovskaja LN, Gusev AN. Enhancement of hyperthermic anti-tumor effect by selective alteration of tumour cells environment. In: Sugahara T, Saito M, editors. Hyperthermic oncology. Vol. 1. London: Taylor & Francis; 1989. pp 146–147.
27. Hiraoka M, Hahn GM. Changes in pH and blood flow induced by glucose, and their effects on hyperthermia with or without BCNU in RIF-1 tumours. Int J Hyperthermia 1990;6:97–103.
28. Horsman MR, Sampson LE, Chaplin DJ. Overgaard J. The *in vivo* interaction between flavone acetic acid and hyperthermia. Int J Hyperthermia 1996;12:779–789.
29. Horsman MR, Murata R, Overgaard J. Improving local tumor control by combining vascular targeting drugs, mild hyperthermia and radiation. Acta Oncol 2001;40:497–503.
30. Fisker RV, Horsman MR, Overgaard J. Hydralazine induced changes in tissue perfusion and radiation response in a C3H mammary carcinoma and mouse normal tissues. Cta Oncol 1991;30:641–647.
31. Cliffe S, Taylor ML, Rutland M, Baguley BC, Hill RP, Wilson WR. Combining bioreductive drugs (SR 4233 or SN 23862) with the vasoactive agents flavone acetic acid or 5,6-dimethylxanthenone acetic acid. Int J Radiat Oncol Biol Phys 1994;29:373–377.

32. Hill SA, Sampson LE, Chaplin DJ. Anti-vascular approaches to solid tumour therapy: Evaluation of vinblastine and flavone acetic acid. Int J Cancer 1995;63:119–123.
33. Dark GD, Hill SA, Prise VE, Tozer GM, Pettit GR, Chaplin DJ. Combretastatin A-4, an agent that displays potent and selective toxicity towards tumor vasculature. Cancer Res 1997;57:1829–1834.
34. Lash CJ, Li AE, Rutland M, Baguley BC, Zwi LJ, Wilson WR. Enhancement of the anti-tumour effects of the antivascular agent 5,6-dimethylxanthenone-4-acetic acid (DMXAA) by the combination with 5-hydroxytryptamine and bioreductive drugs. Br J Cancer 1998;78:439–445.
35. Murata R, Overgaard J, Horsman MR. Comparative effects of combretastatin A-4 disodium phosphate and 5,6-dimethylxanthenone-4-acetic acid on blood perfusion in a murine tumour and normal tissues. Int J Radiat Biol 2001;77:195–204.
36. Siemann DW, Chaplin DJ, Horsman MR. Vascular targeting therapies for treatment of malignant disease. Cancer 2004;100:2491–2499.
37. Kallinowski F, Moehle R, Vaupel P. Substantial enhancement of tumor hyperthermic response by tumor necrosis factor. In: Sugahara T, Saito M, editors. Hyperthermic oncology. Vol. 1. London: Taylor & Francis; 1989. pp 258–259.
38. Lin JC, Park HJ, Song CW. Combined treatment of IL-α and TNF-α potentiates the antitumour effect of hyperthermia. Int J Hyperthermia 1996;12:335–344.
39. Griffin RJ, Lee SH, Rood KL, Stewart MJ, Lyons JC, Lew YS, Park H, Song CW. Use of arsenic trioxide as an antivascular and thermosensitizing agent in solid tumors. Neoplasia 2000;2:555–560.
40. Griffin RJ, Monzen H, Williams BW, Park H, Lee SH, Song CW. Arsenic trioxide induces selective tumour vascular damage via oxidative stress and increases thermosensitivity of tumours. Int J Hyperthermia 2003;19:575–589.
41. Eikesdal HP, Bjerkvig R, Dahl O. Vinblastine and hyperthermia target the neovasculature in BT_4AN rat gliomas: Therapeutic implications of the vascular phenotype. Int J Radiat Oncol Biol Phys 2001;51:535–544.
42. Murata R, Overgaard J, Horsman MR. Potentiation of the anti-tumor effect of hyperthermia by combining with the vascular targeting agent 5,6-dimethylxanthenone-4-acetic acid. Int J Hyperthermia 2001;17:508–519.
43. Eikesdal HP, Schem BC, Mella O, Dahl O. The new tubulin inhibitor combretastatin A-4 enhances thermal damage in the BT_4An rat glioma. Int J Radiat Oncol Biol Phys 2000;46:645–652.
44. Eikesdal HP, Bjerkvig R, Mella O, Dahl O. Combretastatin A-4 and hyperthermia; A patent combination for the treatment of solid tumors. Radiother Oncol 2001;60:147–154.
45. Murata R, Overgaard J, Horsman MR. Combretastatin A-4 disodium phosphate: A vascular targeting agent that improves the anti-tumor effects of hyperthermia, radiation and mild thermoradiotherapy. Int J Radiat Oncol Biol Phys 2001;51:1018–1024.
46. Sakaguchi Y, Maehara Y, Baba H, Kusumoto T, Sugimachi K, Newman RA. Flavone acetic acid increases the antitumor effect of hyperthermia in mice. Cancer Res 1992;52:3306–3309.
47. Maxwell RJ, Nielsen FU, Breidahl T, Stødkilde-Jørgensen H, Horsman MR. Effects of combretastatin on murine tumours monitored by ^{31}P MRS, ^{1}H MRS and ^{1}H MRI. Int J Radiat Oncol Biol Phys 1998;42:891–894.
48. Overgaard J, Bichel P. The influence of hypoxia and acidity on the hyperthermic response of malignant cells *in vitro*. Radiol 1977;123:511–514.
49. Overgaard J, Nielsen OS. The role of tissue environmental factors on the kinetics and morphology of tumor cells exposed to hyperthermia. Ann NY Acad Sci 1980;335:254–280.
50. Overgaard J. Rationale and problems in the design of clinical trials. In: Overgaard J, editor. Hyperthermic oncology. Vol. 2. London: Taylor & Francis; 1985. pp 325–338.
51. Nielsen OS, Horsman M, Overggard J. A future for hyperthermia in cancer treatment?: An editorial comment. Eur J Cancer 2001;37:1587–1589.
52. Horsman MR, Overgaard J. Overcoming tumour radioresistance resulting from hypoxia. In: Steel GG, editor. Basic clinical radiobiology for radiation oncologists. 3rd ed. London: Edward Arnold; 2002. pp 169–181.
53. Der Zee J, Gonzalez Gonzalez D, van Rhoon GC, van Dijk JD, van Putten WC, Hart AA. Comparison of radiotherapy alone with radiotherapy plus hyperthermia in locally advanced pelvic tumours: A prospective, randomized, multicentre trial. The Lancet 2000;355:1119–1125.
54. Durand RE. Keynote address: The influence of microenvironmental factors on the activity of radiation and drugs. Int J Radiat Oncol Biol Phys 1991;20:253–258.
55. Dewhirst MW, Prosnitz L, Thrall D, Prescott D, Clegg S, Charles C, MacFall J, Rosner G, Samulski T, Gillette E, La Rue S. Hyperthermic treatment of malignant diseases: Current status and a view toward the future. Semin Oncol 1997;24:616–625.