Interaction of Heat with Radiation and Chemotherapy

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Abstract

In using hyperthermia in the clinic, thermal dosimetry is essential and is discussed in terms of equating time-temperature relationships for an isoeffect to an equivalent time at a reference temperature, 43° for example. In applying time-temperature equivalence, the sequence between heat and radiation and between two heat treatments, radiation dose rate, linear energy transfer, and physiological parameters must be considered. Furthermore, thermal tolerance observed for both heat killing and heat radiosensitization, especially for doses of 400 rads or greater, may be considered as a thermal dose modifier. When hyperthermia is combined with drugs, most of the factors mentioned above are probably important and need careful evaluation, including the applicability of calculating equivalent time at a reference temperature. Examples are given for delayed heat sensitization after depletion of intracellular polyamines and for heat partially overcoming resistance to 1,3-bis-2-chloroethylnitrosourea in order to illustrate the importance of understanding heat effects on formation of reactive drug intermediates, permeability of drugs into cells, and damage to target molecules.

Introduction

Combined hyperthermia, radiation, and chemotherapy are being investigated for treatment of cancer with encouraging Phase I and II clinical trials. The biological rationale for this approach has been reviewed previously (4, 6). This review will consider concepts of thermal dosimetry and factors affecting interactions, including a brief description of mechanisms, in order to apply hyperthermia most effectively in the clinic.

Thermal Dosimetry

Since thermal damage increases as the time at the elevated temperature increases, and not according to the amount of energy absorbed, as for radiation, our approach to thermal dosimetry involves time-temperature relationships (26). This thermodynamic approach can most easily be explained by the observation that the time required for an isoeffect at temperatures above 43° must be decreased by a factor of 2 when the temperature is elevated 1°. In most in vitro and in vivo systems examined, this relationship changes at about 43° where the factor of 2 in time is related to a change of 0.35–0.5° (8, 26). This change at about 43° is described as a break in the Arrhenius plot. With these time-temperature relationships, any time at any temperature can be related to an equivalent time at 43°, for example, as shown by the nomogram in Chart 1. Of course, any other reference temperature could also be chosen, but 43° should be quite appropriate for clinical applications. Using this approach, a computer program has been written to integrate the changes in time-temperature relationships over a period of time in order to account for the fact that the temperature does not instantaneously increase to the desired level and cannot usually be maintained at a constant temperature. This approach should apply for thermal damage expressed as heat killing and should be approximately correct for heat radiosensitization as well, i.e., to within about a 20% accuracy (26–28). How this relationship will apply to heat combined with chemotherapy is yet to be determined.

As discussed (26), there are complications in applying this unit of equivalent time at 43°. These complications involve the development of thermotolerance, which is similar to dose-modifying factors applied to the use of radiation; step-down heating, in which the thermal inactivation rate at a low temperature increases after a prior exposure at a high temperature (can be accounted for by eliminating the breakpoint at 43°); and other physiological parameters such as low pH and nutrient deprivation, which are not too much unlike modifications of radiation damage related to oxygen, LET, and other factors (3). Although many experiments applying this thermal dosimetry concept need to be carried out both in vitro and in vivo, this thermodynamic approach is a starting point for comparing different time-temperature combinations. With the use of the computer at the time the hyperthermic treatment is being delivered, a "live" time calculation of equivalent minutes at 43° can be obtained in order to determine when the prescribed dose is reached. This should be most important for normal tissues in which a certain amount of normal tissue damage cannot be exceeded.

Effects of Sequence, Dose Rate, LET, and Physiological Parameters on Heat Combined with Radiation

As is well-documented, the maximum cytotoxic effect is observed when radiation is delivered simultaneously with heat, i.e., during the heating interval (4). If radiation is delivered first, repair of radiation damage interacting with the hyperthermic damage can occur, and if heat is delivered first, repair of the heat damage interacting with radiation damage can occur. Results (20) in Chart 2 indicate that this phenomenon correlates well with the amount of unrepared DNA strand breaks. The kinetics for repair of radiation damage are relatively independent of the radiation dose, but the rate of repair of the heat damage decreases as the heat damage is increased, either by increasing the temperature, or by extending the time at the elevated temperature, or by decreasing the pH during the treatment (4, 9, 27). How variations in this sequence can affect the therapeutic ratio has been discussed previously (4). Also, see Ref. 3 for a review of mechanisms involved in hyperthermic radiosensitization.

As is expected, the interaction of hyperthermia with radiation is less synergistic for high-LET radiation than for low-LET radia-

1 Presented at the Workshop on Hyperthermia in Cancer Treatment, March 19 to 21, 1984, Tucson, AZ. This research was supported in part by National Cancer Institute Grants CA 31813, CA 31808, CA 13825, and CA 31867.

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3 The abbreviations used are: LET, linear energy transfer; TER, thermal enhancement ratio; BCNU, 1,3-bis-2-chloroethylnitrosourea.
enhancement ratio at the 10% survival level was not clearly
30 min was delivered immediately prior to radiation (12), the TER
of difference in the thermal enhancement between the low and
the radiosensitizing effect was the greatest for the low dose rate
heating interval; when heat immediately preceded irradiation,
on the dose rate and total dose. In a later study (16) in which
of the heat changed because its duration was equal to that
ation was delivered during the heating interval, the radiation effect
considerable study before a clear picture emerges. When radia-
Radiation than for low-LET radiation.
that the localization of heat in the tumor region where the Bragg
ve that the plateau region than in the Bragg peak. This means
Bragg peak and part of the plateau would be unadvisable,
reducing the selective effect of radiation in the Bragg peak region.
In other words, uniform heating of a region encompassing the
heat killing combined with only a very small increase in the slope
of the radiation survival curve. Therefore, with this greater effect
heat, heat could have a deleterious effect when combined with high-LET radiation by
reducing the selective effect of radiation in the Bragg peak region.
in order to elucidate these complex relationships. Conceivably, the
amount of heat and on the sequence (21, 25). Especially for low
amounts of heat and before, during, and possibly after radiation at different dose rates in
in vivo systems (for review, see Refs. 5 and 14). Furthermore, an example of thermal
Importance of Thermal Tolerance for Heat Combined with
In general, the physiological factors such as low pH and low
nutrient levels, which increase heat killing, also increase heat
radio sensitization (18). Hypoxia itself has been shown to have
no effect on heat killing or heat radiosensitization (for review, see Refs. 5 and 14).

Thermal tolerance for both fractionated and chronic heat treatments has been shown in many in vitro and in vivo systems (for review, see Refs. 5 and 14). Furthermore, an example of thermal tolerance for heat radiosensitization has been demonstrated (17) when heat combined with radiation was delivered 10 hr after an initial heat dose (Chart 3). As seen in this chart, and as reported

Chart 1. Nomogram relating time at any temperature to an equivalent time at 43°C. (see Chart 2). The 2 vertical dashed lines show the time of heat treatment, and the individual points are plotted to show the time of irradiation in relationship to the heat treatment. The points to the right of the vertical dashed lines represent irradiation prior to heat; the points between the dashed lines, samples irradiated during the heat treatment; and the points to the right, cells irradiated after heat. The values shown are relatives to a value of 1.0 for cells that received irradiation alone and 8 hr of repair. No DNA strand breaks were detected in cells in which received heat alone. O, average of 3 independent determinations; bars, S.D. Data are from Ref. 20.

Chart 2. Effect of varying the sequence of heat and radiation on the relative levels of unrepair ed DNA strand breaks. CHO cells were either irradiated with 5000 rad of 250-kVp X-rays or treated for 1 hr at 43°C and then given the alternative treatment at various times afterward. Cells were maintained at 37°C between the 2 treatments. In all cases, the cells received a total of 8 hr of postirradiation incubation at 37°C. The 2 vertical dashed lines show the time of heat treatment, and the individual points are plotted to show the time of irradiation in relationship to the heat treatment. The points to the right of the vertical dashed lines represent irradiation prior to heat; the points between the dashed lines, samples irradiated during the heat treatment; and the points to the right, cells irradiated after heat. The values shown are relatives to a value of 1.0 for cells that received irradiation alone and 8 hr of repair. No DNA strand breaks were detected in cells cells which received heat alone. O, average of 3 independent determinations; bars, S.D. Data are from Ref. 20.

The effects of hyperthermia on low dose rate radiation need
considerable study before a clear picture emerges. When radiation
was delivered during the heating interval, the radiation effect
was greatly enhanced when the dose rate was reduced from
360 down to 3 rad/min (1). However, in this study, the duration of the heat changed because its duration was equal to that
required to deliver the radiation dose, which changed depending on
the dose rate and total dose. In a later study (16) in which the duration of hyperthermia was constant at 41°C for 6 hr, the
radio sensitizing effect was not a great deal different at 90 rad/
min than at 3 rad/min when the radiation was delivered during the
heating interval; when heat immediately preceded irradiation,
the radiosensitizing effect was the greatest for the low dose rate
radiation. Nevertheless, in this study there was not a great deal
of difference in the thermal enhancement between the low and
high dose rate radiation. Then, in another study in which 43°C for
30 min was delivered immediately prior to radiation (12), the TER
enhancement ratio at the 10% survival level was not clearly
related to dose rate. For example, the TER decreased from
about 1.6 to 1.2 as the dose rate decreased from 300 to 6 rad/
min, but increased again to 1.6 as the dose rate decreased further to 0.6 rad/min. Clearly, much work is needed in this area
for different time-temperature relations and different sequences.
One important question is, how long does the hyperthermic
effect persist when it is given prior to low dose rate radiation in
order for it to continually enhance the effect of radiation delivered at later and later times during the treatment period? One would
expect the heat to reduce the amount of recovery of sub lethal
radiation damage, but this has been shown to depend on the
amount of heat and on the sequence (21, 25). Especially for low
thermal doses, the reduction in sublethal radiation damage seems to be greatest when the heat follows the radiation dose.
Therefore, carefully designed experiments need to be carried out
in which different amounts of hyperthermia are delivered before,
during, and possibly after radiation at different dose rates in
order to elucidate these complex relationships. Conceivably, the
clinical results obtained with hyperthermia and brachytherapy
appear to be best, primarily because the best heat distribution
can be obtained with interstitial hyperthermia implants.

In general, the physiological factors such as low pH and low
nutrient levels, which increase heat killing, also increase heat
radio sensitization (18). Hypoxia itself has been shown to have
no effect on heat killing or heat radiosensitization (for review, see Refs. 5 and 14).
Moreover, since the amount of heat radiosensitization increases as the amount of heat killing increases (18) (Chart 3), one would expect to have less heat radiosensitization with fractionated doses if complete repair of the heat effect had occurred (which was not observed by 10 hr in Chart 3) and if tolerance to the subsequent heat dose had occurred. This would be expected if thermal tolerance existed only for heat killing and not for heat radiosensitization. Furthermore, since tumors can be at a lower pH than normal tissue, the amount of tolerance in certain tumor cells may be less than in cells in normal tissue, because the amount of tolerance developing has been reported to be reduced by low pH between the 2 heat treatments (13). Also, the decay of tolerance may be different in tumor from that in normal tissue (6, 19) because of differences in proliferation rates which may provide for more rapid decay of tolerance in the more rapidly proliferating tissues. However, considerable work is needed in this area in which the decay of thermal tolerance is related to proliferation rates, pH, and nutrient levels.

A phenomenon probably related to thermotolerance has been observed in vivo (22, 24). For example, the heating duration required for a TCD-50 when hyperthermia is delivered several hr after a single radiation dose is greatly increased if the heat dose is delivered in 2 fractions separated by 16 hr. This concept could easily apply for a series of radiation doses followed by a series of hyperthermia doses, because the hyperthermia doses following the first should be increased in order to get significant hyperthermic killing. In other words, the concept of increasing subsequent heat doses must be seriously considered. However, another approach can be taken as shown in Chart 4. In this study, Overgaard observed that with 5 fractions (each consisting of radiation and heat) separated by 24 hr, the effect (TER for a TCD-50) was no greater than if the same heat dose had been

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**Table 1**

<table>
<thead>
<tr>
<th>Dose (Gray)</th>
<th>200 rads</th>
<th>600 rads</th>
</tr>
</thead>
<tbody>
<tr>
<td>$X$</td>
<td>0.50</td>
<td>5.00</td>
</tr>
<tr>
<td>$\Delta X$</td>
<td>0.15</td>
<td>2.8 x 10^{-4}</td>
</tr>
<tr>
<td>$\Delta$</td>
<td>0.15</td>
<td>8 x 10^{-4}</td>
</tr>
<tr>
<td>$\Delta \rightarrow \Delta X$</td>
<td>0.05</td>
<td>1.3 x 10^{-4}</td>
</tr>
</tbody>
</table>

$\Delta$, 15 min at 45.5°; t, 10 hr.

for chronic hyperthermia at 42°-42.5° for several hr preceding irradiation (18), the primary effect of thermotolerance is on the slope of the radiation survival curve, and not on the shoulder or the D$_0$. Therefore, this phenomenon of thermal tolerance is probably not very important for fractionated radiation doses in the 200- to 300-rad range. For example (Table 1), survival from 200 rads normalized for heat killing is 0.50 for radiation alone, 0.15 for one heat dose either 10 min or 10 hr prior to radiation, and 0.05 for the 2 heat doses separated by 10 hr prior to radiation. Thus, the second heat dose has definitely enhanced the radiation effect more than that observed after the first heat dose. However, for 600 rads, the opposite is true; survival normalized for heat killing is 2.2 x 10^{-2} for radiation alone, 2.8 x 10^{-5} for one heat dose 10 min prior to radiation, 8 x 10^{-4} for one heat dose 10 hr prior to radiation, and 1.3 x 10^{-4} for the 2 heat doses separated by 10 hr. Thus, for a relatively large radiation dose of 600 rads, the second heat dose has definitely enhanced the radiation effect less ($S = 1.3 x 10^{-4}$) than that observed after the first heat dose ($S = 2.8 x 10^{-5}$), which implies that thermal tolerance for heat radiosensitization should be observed for large radiation doses.

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**Chart 4.** Fractionated radiation and heat in C3H mammary carcinoma. TER after 5 fractions of simultaneous (top) and sequential (bottom) radiation and hyperthermia (42.5°/60 min/fraction) as a function of fractionation interval. The TER is based on the TCD-50 for the mouse mammary carcinoma; bars, 95% confidence limits. The hatched area represents the 95% confidence limits of TER values obtained with a similar single treatment (one radiation dose). Data are from Ref. 24.

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given only once with a single radiation dose. However, when the fractionation interval was increased to about 5 days, supposedly allowing thermotolerance to decay, the effect of the subsequent heat doses was greatly increased. In this type of study, the effects of heat killing as distinct from heat radiosensitization (6, 18) cannot be clearly resolved. Nevertheless, the protocol involving simultaneous heat and radiation should presumably involve some thermal tolerance for heat radiosensitization as well as for heat killing. However, this apparent thermal tolerance for heat radiosensitization may result, in part at least, from less heat radiosensitization because of repair of heat damage from the first dose followed by less heat damage from the second dose, which occurs because of thermal tolerance for cell killing developing by 24 hr between the fractions.

Other interesting observations (Table 2) related to thermal tolerance are evident in this study (23). For the 24-hr fractionation schedule, with the same heat treatment either simultaneously with or sequentially with the last fraction only, the TER was 1.42 and 1.35, respectively, i.e., about the same as for the sequential treatment with each of five 890-rad fractions (TER = 1.37) and as for the one 3690-rad sequential treatment (TER = 1.52). This implies that 4 of the 5 heat doses had no effect and were therefore wasted, which is consistent with thermal tolerance existing after the first heat fraction, at least for heat killing which should be the predominant effect for the sequential protocol where heat and radiation are not interacting. However, the reduction of the TER from 2.62 for the simultaneous treatment with each of five 460-rad fractions to 1.42 for the simultaneous treatment with only the last of five 902-rad fractions implies that there was less thermal tolerance for heat radiosensitization (simultaneous treatment where heat and radiation interact) than for heat killing (sequential treatment). This would be expected from the in vitro results (see Chart 3) where thermal tolerance for radiosensitization was observed only for the slope and not for the shoulder of the radiation survival curve. However, for the large fractions used (460 to 860 rads), some thermal tolerance for heat radiosensitization would be expected for the simultaneous treatments, as suggested both by the in vitro data (Chart 3 and Table 1) and by the increases in vivo in the TER with a 3- or 5-day fractionation interval (Chart 4), supposedly because thermal tolerance had decayed. However, these interpretations may be complicated somewhat by changes in the hypoxic fraction in the tumor. For example, the decrease in the TER with a 7-day fractionation interval, which should allow some repopulation, may be related to a reduction in the fraction of chronically hypoxic cells which have been shown to be selectively killed and possibly radiosensitized by hyperthermia (7).

As shown in Table 2 and Ref. 23, a therapeutic gain for tumor compared to skin was observed for one sequential fraction (1.50), five 24-hr sequential fractions (1.18), four 24-hr fractions (radiation only) with one sequential last fraction (1.41), and four 72-hr sequential fractions (1.37). The therapeutic gain was not reported for the 5- and 7-day fractionation intervals.

Increase of Heat Sensitivity by Depletion of Intracellular Polyamines

Fuller and Gerner (10) reported that the treatment of Chinese hamster ovary cells with α-difluoromethylomithine, which depletes the intracellular polyamines, sensitizes the cells to heat several hr after treatment. In fact, some cell division seemed to be required for this delayed heat sensitization. We have confirmed these results4 and related the heat sensitization to decreased levels of spermidine (Chart 5). Although the increase in heat sensitivity did not occur until several hr after the levels of intracellular spermidine had been greatly reduced, the recovery of the normal heat response correlated precisely with the recovery of normal spermidine levels. Also, both occurred earlier if the cells were treated with low levels of putrescine, a precursor of spermidine (10) (data not shown). Therefore, the hypothesis is that polyamines are sequestered in certain compartment(s) of the cell, such as the cytoskeleton and membranes, or in association with DNA, and that a period of time is required to deplete the polyamines in the particular compartment(s) associated with the manifestation of heat damage. Thus, an understanding of the compartmentalization of polyamines after treatment with α-difluoromethylomithine should be very important in understanding mechanisms of heat damage. But most important for our discussion at present is the relationship of polyamine depletion with possible clinical applications, because this delayed sensitization does not occur as readily in slowly proliferating plateau-phase cultures. Therefore, this delayed heat sensitization could conceivably have a selective effect on rapidly dividing tumor cells relative to slowly dividing normal tissue.

Heat and Chemotherapy

As has been observed for heat and radiation, chemotherapy in most cases has the greatest effect when administered during the heating interval (2, 14). Furthermore, complications can occur because, for drugs such as Adriamycin or actinomycin D, heat prior to the administration of the drug can actually increase the resistance of the cell to the chemotherapeutic agent. Therefore, when chemotherapy is combined with hyperthermia, a careful assessment of optimal sequence is needed.

In understanding mechanisms involved in hyperthermic enhancement of cytotoxicity of chemotherapeutic agents, the kinetics of formation of active products necessary for drug toxicity should be ascertained. This is illustrated with the drug BCNU which alkylates DNA after the formation of reactive alkylating intermediates (30). Since the rate of formation of the alklylation product is very rapid compared to the rate of formation of the reactive intermediate (30), the amount of reactive intermediate as a function of duration of treatment with the drug is most

| X | X | X | X | X | 1220 | 1.0 | 1.0 |
| XΔ | XΔ | XΔ | XΔ | XΔ | 860 | 1.35 | 1.41 |
| X | X | X | X | X | 484 | 2.62 | 0.85 |
| X | X | X | X | X | 860 | 1.42 | 1.05 |

4 TER for tumor/TER for skin; XΔ, rad heat; Δ, rad and heat simultaneously.
significant. The amount of reactive intermediate (ΔC) is shown by the following:

\[ ΔC = C_0(1 - e^{-k_2t}) \]

in which \( C_0 \) is the initial concentration of the drug, and \( k_2 \) is the decay rate of the drug during the time of treatment. The amount of the product (\( P \)) is equal approximately to \( ΔC \). Note that the amount of \( ΔC \) is different than the average concentration (\( \bar{C} \)) shown by the following:

\[ \bar{C} = C_0 \int_0^t e^{-k_2t} \, dt / \int_0^t dt \]

where

\[ \bar{C} = C_0(1 - e^{k_2t})/k_2t \]

but is related to \( ΔC \) by the factor \( 1/k_2t \). The application of this concept of reactive intermediates is shown with the following experimental data obtained with a drug-resistant and a drug-sensitive cell line. As shown in Chart 6, the drug-sensitive cell line (Chart 6A) has the same heat sensitivity as the drug-resistant cell line (Chart 6B). However, when the 2 cell lines are treated with BCNU for 1 hr at various temperatures, the effect of the drug is enhanced more on the resistant cell line than on the sensitive cell line (Chart 7). When survival is plotted (Chart 8) as a function of the amount of reactive intermediate or product formed (\( ΔC \)), as determined from measurements of rates of drug decay, the effect of hyperthermia on the sensitive cell line is mainly an effect on increasing the rate at which the reactive intermediates are formed. However, for a given concentration of reactive products, there is still some enhancing effect of hyperthermia, which means that hyperthermia apparently increases somewhat the rate of the subsequent alkylation reactions in the sensitive cell line. In the drug-resistant cell line, on the other hand...

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hand, hyperthermia apparently enhances the subsequent alkyla-
tion reactions even more. Since hyperthermia has been shown
to increase the amount of cross-linking in the DNA, this effect of
hyperthermia on the drug-resistant line is probably related to
an increase in the number of cross-links in the DNA. Further
studies of this type on the rates of formation of the reactive
intermediates, both in the medium and inside the cell, as well as
on the rates of cross-linking, should provide information impor-
tant for understanding mechanisms involved in drug resistance.

Another factor that may be important in combining heat with
chemotherapy is the pH of the tumor relative to normal tissue.
Lowering the pH not only enhances the heat killing of mammalian
cells (4) but, as shown by Hahn and Shiu (15), also greatly
enhances the killing effect of BCNU. Again, an understanding of
the pH effect on formation of reactive products and on alkylating
reactions, such as DNA cross-links, would be very important for
understanding mechanisms of pH sensitization. These concepts
may indeed have relevance to treatments in vivo, because many
tumors contain cells at low pH, but more importantly, can be
brought to a low pH by glucose infusions. This concept was
used by Urano et al. (29) in selectively enhancing the effect of
cyclophosphamide, an alkylating agent, on mouse tumors, sup-
posedly because the glucose infusions lowered the pH in the
tumors.

These are only a few examples of approaches being taken in
combining heat with chemotherapy. Certainly, many more ap-
proaches, including the use of liposomes, to selectively target
the drug to heated tumor regions, will be forthcoming in the near
future.

* P. Tofflon, unpublished data.
Summary

The effectiveness of both radiation and chemotherapy can be greatly enhanced by applying hyperthermia as a combined therapy. In certain cases, at least, drug resistance may be partially overcome by combining hyperthermia with chemotherapy. The challenge is to exploit any possible differences between the cells in tumor and normal tissue in the development and decay of thermal tolerance, cell cycle kinetics which may enable one to exploit differential sensitivities during the cycle to the agents, and physiological parameters, in order to use the proper sequence and fractionation interval to obtain a thermal gain for the tumor relative to the surrounding normal tissue. In many cases, such a biological rationale will be essential because the tumor and its surrounding and infiltrating normal tissue will be at the same temperature. Obviously, selective heating of the tumor relative to the surrounding normal tissues should provide a therapeutic gain when heat is combined with radiation and chemotherapy.

Studies of the interactions of hyperthermia with radiation and chemotherapy should emphasize several specific points. The applicability of the thermal dose concept, i.e., equivalent time at 43°C, needs to be evaluated for heat combined with radiation and chemotherapy. Data on heat combined with low dose rate radiation is needed. Heat combined with high-LET radiation may eliminate the selective effect of radiation in the tumor region. Should hyperthermia be delivered with radiation in the interactive mode (close together to get both heat killing and heat radiosensitization) or in the noninteractive mode (separated in time to get heat killing in addition to killing from radiation alone)? Does thermal tolerance for heat radiosensitization exist, and if so, how does it compare with thermal tolerance for heat killing in terms of magnitude, kinetics, and being affected by low pH, etc.? When should heat and drugs be delivered in the interactive mode, such as heat and BCNU to overcome drug resistance, or in the noninteractive mode, such as α-difluoromethylornithine and heat to take advantage of delayed heat sensitization? Finally, the mechanisms of heat-drug interactions need to be understood in terms of pharmacokinetics, reactive intermediates, permeability into the cell, and damage to target molecules.

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Cancer Res 1984;44:4714s-4720s.

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