HOTON-ACTIVATION THERAPY

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ABSTRACT

Photon Activation Therapy (PAT) is a technique in which radiation dose to tumor is enhanced via introduction of stable $^{127}$I in the form of iodinated deoxyuridine (IdUrd). As with Neutron Capture Therapy (NCT), stimulation of cytotoxic effects from IdUrd is accomplished by activation with external (or implanted) radiation sources. Thus, accumulations of this nucleoside in actively competing cell pools such as bone marrow and intestinal epithelium do not preclude therapy in so far as such tissues can be excluded from the radiation field.

We have evaluated the several halogenated deoxyribonucleosides, and found IdUrd to be the only thymidine (Tyd) analog providing effective photoactivation in situ. Calculations show that 5% replacement of Tyd in tumor DNA should enhance the biological effectiveness of a given photon radiotherapy dose by a factor of $\sqrt{3}$ via stimulation of Auger cascades. Proportionally higher gains would result from higher replacements of Tyd with IdUrd. In addition, biological response is enhanced by chemical sensitization with IdUrd. It is known that effects of radiation are multiplied by factors of $\sqrt{1.5}$ to 3 as replacement of Tyd with IdUrd varies from $\sqrt{10}$ to 50%. In human tumors in vivo replacements of 5% have been reported, while animal experiments have demonstrated significantly higher replacements.

Our data, as well as other information available to date, indicate that damage from photon activation as well as chemical sensitization does not repair. Thus, if PAT can be carried out at low dose rates such as those used in permanent implant therapy, a further increase in therapeutic gain should accrue as normal tissues are allowed to repair and regenerate; it is anticipated that this increase is efficacy should be a factor of from $\sqrt{3}$ to 8.
A samarium-145 source has been developed for PAT, with activating x-ray energies which vary from 38 to 45 keV ($T\beta = 340$ d). The expectation is that previous favorable clinical results with BrdUrd and high energy x-rays can be further improved through the use of IdUrd and protracted irradiations with low energy x-rays from $^{145}\text{Sm}$ or $^{145}\text{Pm}$. In particular, PAT may provide unique advantages at selected sites such as brain, or head and neck tumors.
1. Introduction

Photon Activation Therapy (PAT) is a technique in which radiation dose to tumor is enhanced via introduction of stable $^{127}$I in the form of iodinated deoxyribose (IdUrd). As with Neutron Capture Therapy (NCT), stimulation of cytotoxic effects from IdUrd is accomplished by activation with external (or implanted) radiation sources. Thus, accumulations of this nucleoside in actively competing cell pools such as bone marrow and intestinal epithelium do not preclude therapy insofar as such tissues can be excluded from the radiation field.

In this technique, high LET radiations in the form of Auger electron distributions are generated through photoactivation of stable iodine incorporated in the tumor cell nucleus by exchanging IdUrd with thymidine (Tyd). In addition, biological response is enhanced by chemical sensitization with IdUrd. It is known that sensitization increases the effects of radiation by factors of $\sqrt{1.5}$ to 3 as replacement of Tyd with IdUrd varies from $\sqrt{10}$ to 50%. In human tumors in vivo replacements of 5% have been reported, while animal experiments have demonstrated significantly higher replacements.

Our data, as well as other information available to date, indicate that damage from photon activation as well as chemical sensitization does not repair. Thus, if PAT can be carried out at low dose rates such as those used in permanent implant therapy, a further increase in therapeutic gain should accrue as normal tissues are allowed to repair and regenerate.

We have evaluated the several halogenated deoxyribonucleosides, and found IdUrd to be the only thymidine (Tyd) analog providing effective photoactivation in situ. A formula has been devised with which the therapeutic gain can be calculated by combining both effects of chemical sensitization and stimulation.
of Auger cascades for various % exchanges of IdUrd in DNA. Results show significant advantages may be gained through the use of protracted irradiation with implanted sources.

A samarium-145 source has been developed for PAT, with activating x-ray energies which vary from 38 to 45 keV ($T_{1/2} = 340$ d). The expectation is that PAT may provide unique advantages at selected sites such as brain, or head and neck tumors.

2. Rationale

Table I summarizes characteristics of the different halogens, all of which have been incorporated into thymidine analogs (i.e., halogenated deoxyuridines). We have completed an extensive analysis of the various halogenated deoxyuribonucleosides, in which the photoelectric absorption cross section $\tau$, total Auger electron energy $E_a$, fluorescence yield $\omega$, average number of electrons $n$, and half-value layer (HVL) were taken into account (Reference 1). It was found that the main parameter reflecting response from photon-induced Auger electrons is the ratio of cross sections for photon absorption in normal DNA within the nucleus, and for absorption by the halogen in substuted Tyd analog. This ratio is designated $C$. The linear attenuation coefficients for $H_2O$, Br and I are given in Figure 1 assuming 80% replacement of Tyd by IdUrd or BrdUrd, and a nuclear volume of $100\mu^3$. A value of 80% for replacement is considered to be the upper limit which might be achieved in vivo. It can be seen in Figure 1 that even at this replacement the linear attenuation coefficient for Br is much less than that of DNA (the cross section for normal DNA is assumed to be well approximated by that of water). In other words, the reaction rate (per unit volume) of photon absorptions contributed by Br would be significantly less than the absorption rate in DNA. The reverse is true with I; Figure 1 shows the
attenuation coefficient significantly exceeds that of DNA in the region between the K absorption edge (33.2 keV) and ~60 keV. The ratio
\[ C = \frac{\tau \text{(halogen)}}{\tau \text{(H}_2\text{O}) + \sigma_a \text{(H}_2\text{O})}] \]
is shown as a function of photon energy in Figure 2. This ratio, assuming 100% replacement is 2.6 for I (33 keV) and 0.39 for Br (14 keV) (i.e., a factor of 6.7 in favor of iodine). The ratio C is graphed for 100% replacement to simplify calculations. Clearly, since \( \tau \) is proportional to the cube of the atomic number (Z), the lighter elements, Cl and F, will be less effective. Astatine has a Z of 85, and has been evaluated biologically in the form of 5-astatodeoxyuridine (\(^{211}\)At) (Ref. 2). However, lack of a stable isotope would presumably limit its clinical usefulness. Half-lives for the various isotopes do not exceed 10 hours.

Of the several halogens then, iodine appears to be the only viable choice, if it is hoped to take advantage of stimulated Auger cascades.

3. **Equation for Dose Enhancement**

On the basis of the above evaluation, an equation was developed for calculation of the enhanced dose \( D_E \);

\[ D_E = S \cdot D + C \cdot D \cdot \left( S \cdot \phi_{TOT} + G \cdot \phi_e \cdot F \cdot \phi_0 \right) \]  
(Eq. 1)

where \( D = \) absorbed dose to normal cells in rads,

\( D_E = \) enhanced dose,

\( S = \) radiation sensitization due to low LET radiation,

\( C = \) cross section ratio, described above,

\( \phi_{TOT}, \phi_e = \) fraction of total photoelectric effect energy absorbed locally \( (\phi_{TOT}) \) and of total energy released as primary, Auger, and Coster-Kronig electrons \( (\phi_e) \),

\( G = \) geometrical advantage due to Auger effect in DNA,
\[ F = \text{high LET enhancement due to recovery of normal tissues from effects of low LET radiation, and} \]
\[ O = \text{Oxygen Gain Factor (OGF) of Auger electrons, where OGF is the ratio of OER (oxygen enhancement ratio) for standard 250 kvP x-rays to the test system OER.} \]

The assumption is made that toxicity resulting from Auger radiation is additional to the chemical toxicity and the radiosensitizing effect of the halogenated deoxyribonucleosides. Factors within the brackets of equation 1 represent the incremental dose resulting from Auger cascades. The concepts listed above are detailed in Ref. 1. A brief description of the dose-modifying factors affecting D and CD is given below.

3.1 Radiation Sensitization (S)

Halogenated pyrimidines are effective as radiosensitizing agents. There is evidence of a variation in S of from \( \sqrt{1.6} \) to 3 as replacement varies from \( \sqrt{10} \) to 50\% \( (3) \).

3.2 Ratio of Cross Sections, C: \( (C = \text{cross section of halogen/water}) \)

The linear attenuation coefficient is the parameter which will determine the amount of energy imparted to tissue from the incident photon beam. Clearly, if the probability of direct interaction between the incident beam and IdUrd is insignificant, the second term in Eq. 1 will become negligible (while S will still be effective). The concept of C has been described above and values are shown in Figure 2.

3.3 Fraction of Photon Energy (\( \phi \))

The geometrical factor \( G \) is modified by \( \phi \), the fraction of absorbed energy appearing as the primary and Auger electrons (see Figure 2 where \( \phi \) for I
is plotted). At 35 keV, \( \phi_e \leq 0.43 \), due to \( \sim 80\% \) absorption in the K shell and the relatively high fluorescent yield of 0.87.

Sensitization should result from radiation stimulated in substituted halogens by photoelectric absorption. The bulk of these stimulated emissions have ranges far exceeding the 0.05\( \mu \) radius within which high LET effects would be expected. The fraction \( \phi_{\text{TOT}} \) modifying \( S \) would also include those x-rays absorbed locally.

3.4 Geometrical Advantage (G)

K and L shell vacancies can be initiated by the photoelectric effect in stable iodine. Thus, unlike I-125, the radiotoxicity of the consequent Auger cascades can be restricted to regions within the radiation field. This regionally localized radiation toxicity has been called "Geometric Advantage" (G).

Using various mammalian cell systems, the measured geometrical advantage as reported in the literature varies from 3 to 30 (biological effect of \(^{125}\text{I} \) compared to \(^{3}\text{H}-\text{Tyd} \), or externally or extracellularly produced x-rays). The numbers 3-30 are based on comparison of absorbed dose to the nucleus. Radiation toxicity is such that measurements of G occur at I concentrations below that which produces sensitization.

In the determination of \( D_G \), a value for G of 9 has been used. This value is based on the value of 9.1 determined by Burki et al. (4) by comparing the effects of \(^{125}\text{IdUrd} \) to \(^{3}\text{H}-\text{Tyd} \). The assumption is made here that per unit dose, the effect of Auger cascades stimulated by photoelectric absorption is similar to that resulting from electron capture in \(^{125}\text{I} \). The two mechanisms are not identical, in that electron capture in \(^{125}\text{I} \) is followed by internal conversion of the 35 keV \( \gamma \)-ray. It does not appear unreasonable, however, to assume that
the biological effect will be analogous when compared on the basis of absorbed dose from ejected electrons, as was done here.

3.5 Effects of Recovery during Fractionated or Permanent Implant Therapy

Effects of normal tissue recovery and regeneration during conventional fractionated radiotherapy (30 fractions over 4-6 weeks) increases normal tissue tolerance by a factor of \(\sqrt{3}\) (from \(\sqrt{2000}\) to 6000 rads). It is thought by many therapists that improved results are obtained from "permanent" implants such as I-125 seeds, where repair and regeneration increase normal tissue tolerance by a factor of \(\sqrt{8}\) (see Figure 3) (Ref. 6).

If damage imparted to tumor is non-repairable, effective tumor dose will be augmented by these factors.

3.6 Oxygen Gain Factor (O)

A value for the OER of \(^{125}\)I of 1.4 has been determined (5). The value of 1.4 is a composite one, being a consequence of both Auger electrons and local energy deposition from photons. The OER for Auger electrons alone may be lower. Compared to x-rays (OER \(\sqrt{3}\)), an advantage of 2 is gained. This advantage is that which is generally attributed to high LET radiations since they are less sensitive to such factors as oxygen tension, cell cycle, and dose rate.

4. Radiation Sources

4.1 Samarium-145 Sources

Samarium-145 is an ideal source for photoactivation of \(^{127}\)I. It decays by electron capture, emitting 140 x-rays per 100 disintegrations with energies between 30 and 45 keV, plus 13 \(\gamma\)-rays at 61 keV. Decay with a \(T^{1/2}\) of one year is to \(^{145}\)Pm (\(T^{1/2} = 17.7\) y, with emitted photons in the same energy range as \(^{145}\)Sm) (Table II). Sources of Sm-145 have been made at BNL by irradiating Sm-144. The
measured spectra from one of these sources is shown in Fig. 4; long lived contami-
nations do not appear to present a problem. Anticipated activities are $\sqrt{2.5}$
mCi/mg, with a dose rate of $\sqrt{0.8}$ rads/hr-mCi at 1 cm. Eye plaques are currently
being evaluated in rabbits.

4.2 70 kVp X-rays

The relative constancy of the ratio of cross sections C over the re-
gion between 33 and 60 keV, plus the availability of x-ray machines, suggests
the use of tungsten target x-ray beams. A large fraction of the photons for a
75 kVp beam (2.25 mm Al added filtration) are in the region between 33 and 60
keV. Further, the relative number of photons in the region between 33 and 50
keV can be increased by 50% through the addition of a Gd filter (7). The aver-
age value of C can be obtained by numerical integration over these spectra; when
this is done, and the values weighted for dose, the average value of C for a 75
kVp beam is 1.61 (evaluated at 100% replacement) or 64% of that obtained with a
40 keV monoenergetic beam. Filtering with 0.227 mm Gd would provide 72% of the
effectiveness of a 40 keV beam (see Table III; taken from Ref. 1). Thus it
would appear that 70-80 kVp x-ray beams would be useful for evaluation of radia-
tion enhancement at high dose rates.

5. Radiation Response of Single Cell Cultures

Single cell cultures of V-79 cells were exposed to 70 kVp x-rays filtered
with 1.3 mm Al. The response of normal cells, and cells with 25 and 50% replace-
ment of Tyd with IdUrd is shown in Fig. 5. These are preliminary data, and are
shown only to indicated that radiation enhancement was obtained, and that the
shape of the survival curve is indicative of non-repairable damage.
Irrespective of the relative contribution of sensitization or photoactivation,
it may be possible to enhance this damage by a factor of $\sqrt{3}$ with fractionated
irradiation, or by a factor of 8 with protracted irradiation from "permanent" implants.

Similar curves were obtained with a Cs-137 source ($E_\gamma = 661$ keV). These are shown in Fig. 6 for 50% replacement, and compared to data from the 70 kVp beam. Results are similar, indicating that the major portion of the damage in both Fig. 5 and 6 may be due to sensitization (since the Cs-137 photons are of too high an energy to stimulate Auger cascades efficiently). Most importantly however, the lack of a shoulder indicates that the cell's ability to repair damage caused by sensitization is impaired, as been suggested by others (8).

6. Revised Equation for Dose Enhancement

As a result of the above data, the equation for dose enhancement (Eq. 1) was revised to include the multiplicative factor $F$ for all components of enhanced dose:

$$D_E = F[S\cdot D + C\cdot D (S\cdot \phi_{TOT} + G\cdot \phi_e\cdot 0)]$$

(Eq. 2)

7. Dose Enhancement

Dose enhancement was calculated for bifilar replacements of 5, 25 and 50%, using Eq. 2. Parameter values used are shown in Table IV, and were taken from the text, and/or fig. 2. Values of enhanced dose are shown in fig. 7 for the cases of $F = 1$ (acute dose); $F = 3$ (fractionated radiation) and $F = 8$ (protracted irradiation from "permanent" implants). No weight was accorded to the oxygen gain factor; 0 was kept equal to 1 in these calculations.

The therapeutic gain, as represented by the ratio of enhanced dose over normal tissue dose ($D_E/D$) is impressive, even at 5% replacement. As noted above, 5% replacement of Tyd in tumors has already been measured in humans. Greater average replacements have been obtained in B-16 melanoma in C-57 mice.
(personal communication, Dr. S. L. Commerford, BNL, Upton, N. Y.). The possibility exists that with appropriate blockage of the de novo synthesis of Tyd, replacements of Tyd with IdUrd of up to 25% might be obtained in clinical situations.

8. Summary

It is suggested here that significant advantages should accrue from the use of 40 keV photons from implanted sources of $^{145}$Sm. These energies should stimulate Auger electron cascades from IdUrd, as well as produce non-repairable damage from radiosensitization. The use of low dose rates (~10 rads/hr) should allow repair in normal tissues exposed to the activating photons. Utilization of this technique with brain tumors should minimize problems associated with radiosensitization of normal tissues, as CNS tissues do not synthesize DNA. The deposition of high LET radiations selectively in tumor cells provides unique advantages not available to either conventional therapy or other forms of particle therapy (fast neutrons, protons, pions, heavy ions).
References


<table>
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<tr>
<th>Halogen</th>
<th>Atomic number</th>
<th>Atomic weight</th>
<th>Van der Waals radius (pm)</th>
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<tbody>
<tr>
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<td>135</td>
</tr>
<tr>
<td>Cl</td>
<td>17</td>
<td>35.5</td>
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<tr>
<td>Br</td>
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<tr>
<td>At</td>
<td>85</td>
<td>210.0</td>
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</table>

*From Reference 1.
Table II

145\textsuperscript{Sm} and 145\textsuperscript{Pm} Photon Energies and Abundances*

\begin{tabular}{|c|c|c|c|c|}
\hline
 & \textbf{145\textsuperscript{Sm} (T1/2 = 340d)} & & \textbf{145\textsuperscript{Pm} (T1/2 = 17.7y)} & \\
\hline
\textbf{Photon Energy (keV)} & \textbf{Photons per Disintegration} & \textbf{Photon Energy (keV)} & \textbf{Photons per Disintegration} & \\
\hline
\textbf{x-ray} & 38.2 & 0.384 & \textbf{x-ray} & 36.9 & 0.211 \\
\textbf{\ "} & 38.7 & 0.739 & \textbf{\ "} & 37.4 & 0.386 \\
\textbf{\ "} & 43.8 & 0.222 & \textbf{\ "} & 42.2 & 0.122 \\
\textbf{\ "} & 44.9 & 0.044 & \textbf{\ "} & 43.3 & 0.025 \\
\textbf{\gamma-ray} & 61.4 & 0.127 & \textbf{\gamma-ray} & 67.2 & 0.007 \\
\textbf{\ "} & 1.516 = Total & \textbf{\ "} & 72.4 & 0.022 \\
\textbf{\ "} & 0.773 = Total & & & \\
\hline
\end{tabular}

*From Ref. 1
### TABLE III

Average value of C for various x-ray spectra

\[ C = \frac{\tau(\text{iodine})}{(\tau(H_2O) + a(H_2O))} \]

<table>
<thead>
<tr>
<th>kVp</th>
<th>Added Filtration</th>
<th>C</th>
<th>% Monoenergetic Photon Dose (40 Kev)</th>
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<tr>
<td>50</td>
<td>1 mm Al</td>
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<tr>
<td>75</td>
<td>2.25 mm Al</td>
<td>1.61</td>
<td>64%</td>
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<tr>
<td>75</td>
<td>0.227 mm Gd</td>
<td>1.80</td>
<td>72%</td>
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<tr>
<td>PARAMETER</td>
<td>5%</td>
<td>25%</td>
<td>50%</td>
</tr>
<tr>
<td>-----------</td>
<td>-----</td>
<td>------</td>
<td>------</td>
</tr>
<tr>
<td>( S )</td>
<td>1.5</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>( C )</td>
<td>0.125</td>
<td>0.625</td>
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</tr>
<tr>
<td>( G )</td>
<td>9</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>( \phi_{icot \phi_e} )</td>
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<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>( O )</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>( F )</td>
<td>3 or 8</td>
<td>3 or 8</td>
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Values of Parameters Used in Calculation of Effective Dose \( (D_E) \)
Figure Captions

Fig. 1. Linear attenuation coefficients for H₂O, Br and I. Eighty percent replacement of Tyd of IdUrd or BrdUrd in DNA is assumed. The number of thymine bases in a 100μ₃ cell nucleus was assumed to be $3.23 \times 10^9$. From Ref. 1.

Fig. 2. The ratio of cross sections (C) for absorption in substituted halogen or normal DNA. $C = \left\{ \tau \text{(halogen)} / (\tau \text{(H}_2\text{O}) + \sigma_a \text{(H}_2\text{O)}) \right\}$. One hundred % replacement of Tyd by IdUrd or BrdUrd is assumed. The fraction of total photoelectric effect energy released as primary, Auger, and Coster-Kronig electrons ($\phi_e$) is also plotted as a function of incident photon energy for I. From Ref. 1.

Fig. 3. Skin tolerance to absorbed dose from permanent implants of I-125 (upper curve). For comparison, skin tolerance to acute doses is $\sim 2000$ rads. From Ref. 6.

Fig. 4. Measured photon energy spectra from Sm-145, 28 days from end of bombardment.

Fig. 5. Single cell survival curve for hamster V-79 cells exposed to 70 kVp x-rays (\sim 30 rads/min.). Curves are shown for 0, 25 and 50\% replacement of Tyd in DNA with IdUrd (average or bifilar replacement).

Fig. 6. Single cell survival curve for hamster V-79 cells exposed to 70 kVp x-rays and Cs-137 (\sim 30 rads/min.). Curves are shown for 0 and 50\% replacements of Tyd in DNA with IdUrd (average or bifilar replacements).

Fig. 7. The Dose Enhancement (DE) is the ratio of effective tumor dose or enhanced dose $D_E$ to normal tissue dose $D$. Replacement of Tyd by IdUrd is assumed to be in tumor only.
ATTENUATION COEFFICIENT FOR H₂O, Br AND I

80% REPLACEMENT OF THYMIDINE IN DNA

- ○ = H₂O (τ + σa; cm⁻¹)
- × = I(τ; 2.7 × 10⁹ atoms/cm³ × σ cm²/atom)
- △ = Br(τ; 2.7 × 10⁹ atoms/cm³ × σ cm²/atom)

FIGURE 1
Cancer Lethal Dose

Rodon-222 (8000 rads/10 days)

Skin Tolerance limit

D = 3KT^{0.33}

60 day
Lodine-125
15000 rads

Effective Region

Cancer Lethal Dose

3.8 day
Radon-222
(8000 rads/10 days)

Figure 3
Samarium 145

Counts/Channel (ARB Units)

38.72 keV (73.9%)

38.17 keV (38.4%)

43.8 keV (22.2%)

44.9 keV (4.4%)

61.4 keV (12.7%)

Figure 4
% SURVIVAL OF V-79 CELLS
70 kVp X-RAYS

CONTROL

IdUrd

● 25% REPLACEMENT
△ 50% REPLACEMENT
( PRELIMINARY DATA )

25%

50%

NO IdUrd

% SURVIVAL

ABSORBED DOSE (rads)

FIGURE 5
% SURVIVAL OF V-79 CELLS

- Cs 137 CONTROL
- 70 kVp CONTROL
- Cs-137 50% REPLACEMENT
- 70 kVp 50% REPLACEMENT

(PRELIMINARY DATA)

FIGURE 6
Figure 7

EFFECTIVE TUMOR DOSE
NORMAL TISSUE DOSE
\( \frac{D_E}{D} \)

ACUTE

50% REPLACEMENT

FRACTIONATED

10.5

31.5

5.4

16.3

25% REPLACEMENT

PROTRACTED

84.0

43.5

2.2

6.5

17.3

5% REPLACEMENT