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Laboratory Investigation

Implantable biodegradable polymers for IUdR radiosensitization of experimental human malignant glioma

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Summary

Purpose: The potential of halogenated pyrimidines for the radiosensitization of human malignant gliomas remains unrealized. To assess the role of local delivery for radiosensitization, we tested a synthetic, implantable biodegradable polymer for the controlled release of 5-iodo-2'-deoxyuridine (IUdR) both *in vitro* and *in vivo* and the resultant radiosensitization of human malignant glioma xenografts *in vivo*.

Materials and methods: In vitro: To measure release, increasing (10%, 30%, 50%) proportions (weight/weight) of IUdR in the polyanhydride [(poly(bis(p-carboxyphenoxy)-propane) (PCPP) : sebacic acid (SA) (PCPP : SA ratio 20 : 80)] polymer discs were incubated (1 ml phosphate-buffered saline, 37° C). The supernatant fractions were serially assayed using high performance liquid chromatography. To measure modulation of release, polymer discs were co-loaded with 20 μCi 5-125-iodo-2'-deoxyuridine (125-IUdR) and increasing (10%, 30%, or 50%) proportions of D-glucose. To test radiosensitization, cells (U251 human malignant glioma) were sequentially exposed to increasing (0 or 10 μM) concentrations of IUdR and increasing (0, 2.5, 5.0, or 10 Gy) doses of acute radiation. *In vivo*: To measure release, PCPP : SA polymer discs having 200 μCi 125-IUdR were surgically placed in U251 xenografts (0.1–0.2 cc) growing in the flanks of nude mice. The flanks were reproducibly positioned over a collimated scintillation detector and counted. To measure radiosensitization, PCPP : SA polymer discs having 0% (empty) or 50% IUdR were placed in the tumor or contralateral flank. After five days, the tumors were acutely irradiated (500 cGy × 2 daily fractions).

Results: In vitro: Intact IUdR was released from the PCPP : SA polymer discs in proportion to the percentage loading. After 4 days the cumulative percentages of loaded IUdR that were released were 43.7 ± 0.1, 70.0 ± 0.2, and 90.2 ± 0.2 ($p < 0.001$ ANOVA) for the 10, 30, and 50% loadings. With 0, 10, 30, or 50% D-glucose co-loading, the cumulative release of 125-IUdR from PCPP : SA polymers was 21, 70, 92, or 97% ($p < 0.001$), respectively, measured 26 days after incubation. IUdR radiosensitized U251 cells *in vitro*. Cell survival ($\log_{10}$) was − 2.02 ± 0.02 and − 3.68 ± 0.11 ($p < 0.001$) after the 10 Gy treatment and no (control) or 10 μM IUdR exposures, respectively. *In vivo: 125-IUdR Release*: The average counts ($\log_{10}$ cpm ± SEM) (hours after implant) were 5.2 ± 0.05 (0.5), 4.3 ± 0.07 (17), 3.9 ± 0.08 (64), and 2.8 ± 0.06 (284). *Radiosensitization*: After intratumoral implantation of empty polymer or intratumoral 50% IUdR polymer, or implantation of 50% IUdR polymers contralateral to tumors, the average growth delays of tumors to 4 times the initial volumes were 15.4 ± 1.8, 20.1 + 0.1, and 20.3 + 3.6 (mean + SEM) days, respectively ($p = 0.488$ one-way ANOVA). After empty polymer and radiation treatments, no tumors regressed and the growth delay was 31.1 + 2.1 ($p = 0.046$ vs. empty polymer alone) days. After implantation of 50% IUdR polymers either contralateral to the tumors

or inside the tumors, followed by radiation, tumors regressed; growth delays to return to the initial average volumes of 14.0 + 3.6 or 24.2 + 0.2 ($p < 0.01$) days, respectively.

Conclusions: Synthetic, implantable biodegradable polymers hold promise for the controlled release and local delivery of IUdR for radiosensitization of gliomas.

Introduction

Malignant gliomas comprise half of the 9000 annual new primary brain neoplasms in the United States [1]. Despite intensive research for more effective treatments, these tumors remain refractory to surgery, radiation, and chemotherapy [2–5]. Improved local therapy of malignant gliomas appears warranted. These tumors arise focally, the initial therapy (surgery) is local, and the extent of resection may correlate with survival [6]. Recurrences are focal as well. In 83 percent (29/35) of patients, recurrent tumors were within 2 cm of the contrast-enhancing margin of the pre-morbid CT scan [7]. Fifty-nine of 62 patients had tumor regrowth either within or contiguous to resected area after radiation [8]. Wallner [9] observed that 56% (18/32), 78% (25/32), and 94% (30/32) of recurrent tumors were within 1, 2, or 3 cm of the pre-surgical tumor margin. These high rates of local recurrence emphasize the need for improved local therapy.

Halogenated pyrimidines are potent radiosensitizers. When compared to radiation alone, sequential 5-iodo-2'-deoxyuridine (IUdR) [10] or 5-bromo-2'-deoxyuridine (BUdR) [11] and radiation cause higher killing of human malignant glioma *in vitro*. The extent of sensitization is proportional to the percentage replacement of thymidine in the replicating DNA [12, 13] and is proportionate to the both the magnitude and duration of exposure. In the U87 malignant glioma cell line, increasing (1 to 10 μM) exposures to IUdR cause increasing (12.8 and 32%) thymidine replacement and resultant sensitizer enhancement ratios (1.07 and 1.66) [14]. Recent clinical data suggest that when combined with multiagent chemotherapy, concurrent radiotherapy and intravenous BUdR show promise in the treatment of anaplastic gliomas [15].

Although the principle has been known for over 35 years [16, 17] and the first clinical trial of this strategy for the treatment of malignant gliomas occurred over 25 years ago [18], many factors have prevented further success. After systemic administration, the clearance of halogenated pyrimidines from the blood is rapid [19], toxicity (usually marrow suppression) is high, and the percentage thymidine substitution subsequently measured in biopsied tumors is low [20–30]. The blood-brain barrier may further limit delivery of drugs to brain tumors [31]. The sustained, intratumoral delivery of halopyrimidines could circumvent the blood-brain barrier, diminish systemic exposure, and increase the therapeutic ratio.

Synthetic, biodegradable polyanhydride polymers allow sustained, controlled release of drugs and provide an alternative to systemic administration [32]. Their advantages include predictable degradation by surface erosion, continuous release of drug, and absorption of the polymer by the body that renders removal unnecessary. The products of degradation of the polymer are non-mutagenic, non-cytotoxic, and non-teratogenic [33]. Clinically, polyanhydride polymers have mediated the safe and effective delivery of BCNU to recurrent malignant gliomas [34, 35]. The role of implantable, biodegradable polymers in the local delivery of halogenated pyrimidines for the radiosensitization of human malignant gliomas remains unexplored, however. We therefore tested the release of IUdR from the polyanhydride polymer both *in vitro* and *in vivo* and measured the resultant radiosensitization of a human malignant glioma *in vivo*.

Materials and methods

Cells

The human malignant glioma cell line U251 was obtained from the DCT Tumor Repository, National Cancer Institute, Frederick Cancer Research Facility, Frederick, MD. Cells were cultured in Dulbec-

co's MEM/Ham's F-12 nutrient mixture with 10% fetal bovine serum (GIBCO, Grand Island, NY) and antibiotics (penicillin and streptomycin) in 12 × 80 mm plastic culture dishes or T-25 culture flasks (Falcon Plastics, Cockeysville, MD). Cells were incubated (37° C) and gassed with a mixture of 5% carbon dioxide and 95% air. Media were changed twice weekly and cells were passaged at confluence with 0.5% trypsin.

In vitro *radiosensitivity*

To have log phase growth, cells were trypsinized and replated in triplicate 3 days prior to irradiation in media containing either no (control) or 10 μM IUdR (Sigma, St. Louis, MO). The cells were acutely (1.1 Gy/min) irradiated (AECL Gamma-cell 40 irradiator, Canada) with increasing (0, 2.5, 5.0, or 10 Gy) single fractions.

Immediately after irradiation, the cells were trypsinized, counted, and replated in media having no IUdR in numbers to yield between 20 and 200 colonies per plate. After 10 days, the plates were fixed with methanol and acetic acid, stained with crystal violet and scored for colonies containing more than 50 cells. Radiation survival data from IUdR-treated cells were corrected for plating efficiency in IUdR alone.

Polymer synthesis

Solid IUdR was mixed with PCPP : SA (20 : 80) that was synthesized according to the method of Domb and Langer [36] to give a mixture containing 10, 30, or 50% IUdR by weight. When co-loaded with therapeutic agents in polymers, inert hydrophilic compounds such as D-glucose can increase the rates of hydration and degradation of the polymer [49]. To test modulation of the *in vitro* release of IUdR, solid D-glucose (Sigma, St. Louis, MO) was mixed with PCPP : SA and tracer (20 μCi/10 mg disc) activities of 5-I-125-iodo-2'-deoxyribose (125-IUdR) (ca. 1500 Ci/mmole) (Amersham, Inc., Arlington Heights, IL) to give a mixture containing 10, 30, or 50% D-glucose by weight. To test *in vivo* release, higher (200 μCi/10 mg disc) activities of 125-IUdR were combined with the PCPP : SA.

All mixtures were dissolved in methylene chloride to give a 10% solution (w : v). The solvent was evaporated with a nitrogen stream to yield a dry powder. IUdR or 125-IUdR polymer discs (10 mg final weight) were prepared by compression molding 11 mg of the powder with a stainless steel mold (internal diameter 2.5 mm) under light pressure using a vice.

IUdR release studies: *in vitro*

IUdR release

Groups of at least three polymer discs having increasing (10, 30, or 50%) proportions of unlabeled IUdR were incubated for known intervals in 1 ml of 0.1 M phosphate-buffered saline (PBS) at 37° C. The supernatant was periodically removed, replaced with fresh PBS, and assayed for IUdR by high performance liquid chromatography (HPLC) as previously described [37]. The cumulative percentage of the loaded IUdR that appeared in these serial supernatant fractions was plotted vs. time.

Modulation of IUdR release

Groups of at least three polymer discs having 125-IUdR alone or co-loaded with increasing proportions of D-glucose were incubated in PBS as above. To measure the cumulative percent of loaded 125-IUdR released into the supernatant fractions vs. time we used a calibrated, collimated NaI(T1) scintillation detector as previously described [38].

Animals

All animal experiments were performed in accordance with the guidelines of the Institutional Animal Care and Use Committee. Male nu/nu nude mice, 6 weeks of age, were obtained from the National Cancer Institute (Bethesda, MD), kept in a dedicated

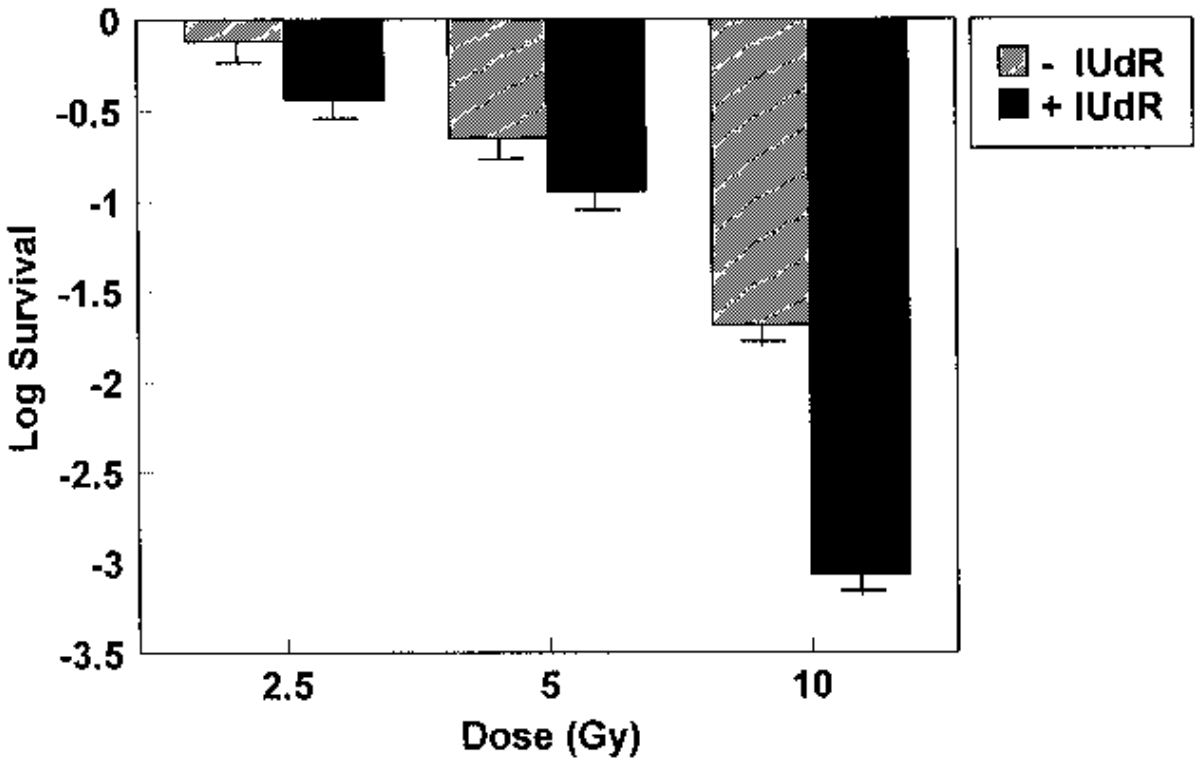

Figure 1. Radiosensitization of U251 human malignant glioma by IUdR *in vitro*. Cells were grown for 3 days in media having 0 or 10 μM IUdR concentrations, acutely irradiated with the indicated doses, and assayed for survival. *Ordinate*: $\log_{10}$ cell survival. *Abscissa*: Dose (Gy) acute radiation. *Bars*: The SEM was less than 5% for all points.

animal facility with 5 mice/cage, and given free access to lab chow and water.

Anesthesia

For surgical procedures, mice were anesthetized with i.p. injections of 2–4 ml/kg of a stock solution containing ketamine hydrochloride (25 mg/ml), xylazine (2.5 mg/ml), and 14.25% ethyl alcohol in normal saline. The mice recovered in their cages following all surgical procedures.

S.C. xenografts

After preparation of the left flanks of 20 mice with 70% ethyl alcohol, subcutaneous injections of 5×10^6 U251 cells were given. Tumors were visible after 1 week. The size range for experimental xenografts was 0.1–0.2 cm^3. The growth of experimental tumors was measured every 3 days using calipers.

In vivo *IUdR release*

For surgical implantation of 125-IUdR polymers, 5 mice had skin incisions placed over the xenograft using a # 11 scalpel blade. For each mouse the 125-IUdR polymer was placed within the tumor to a depth of 3 mm via a single incision, and the wound was closed using surgical staples. To measure the activity (cpm) vs. time (h), the tumors bearing the 125-IUdR polymers or the contralateral control flanks were reproducibly positioned over a collimated scintillation detector and counted for 30 seconds. The decay-corrected activity was plotted vs. time. The observed activity vs. time curves for each ani-

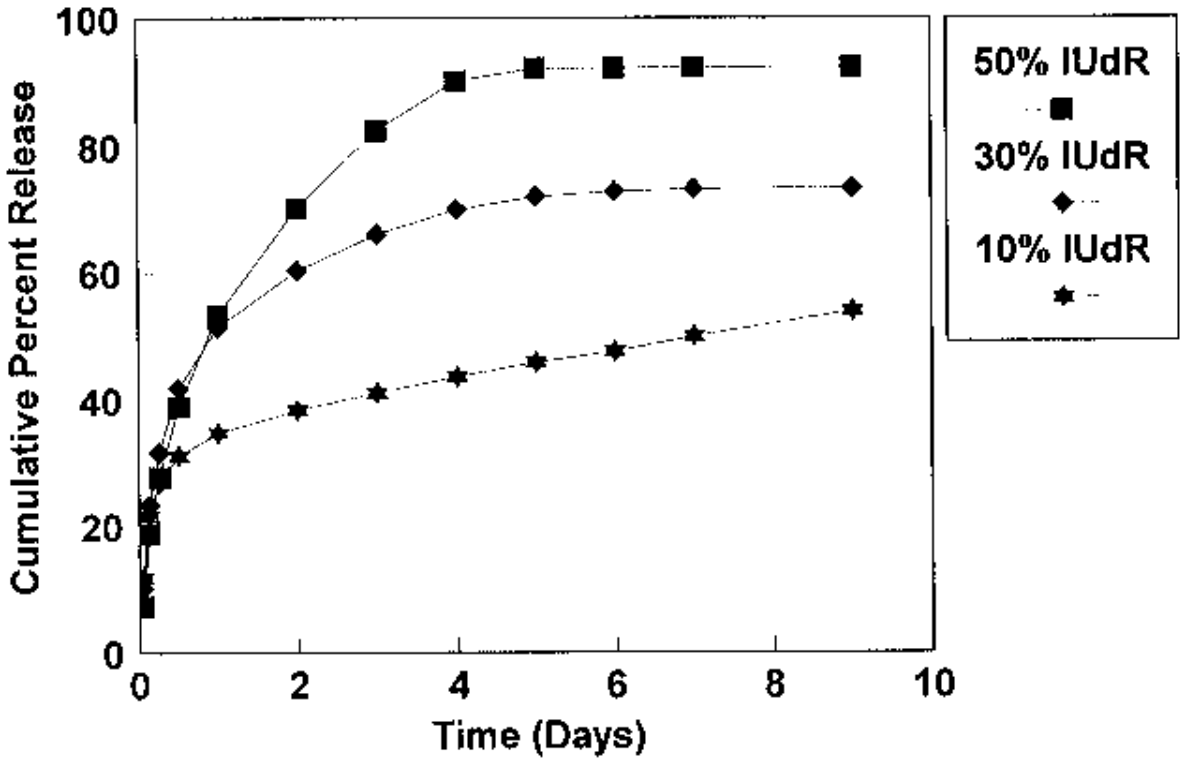

Figure 2. In vitro release profiles of PCPP : SA (20 : 80) polymer discs (10 mg) loaded with IUdR 10, 30, and 50% by weight. *Ordinate*: cumulative IUdR released as a percentage of total drug initially loaded into the polymer. *Points*: mean of 3 measurements. The SEM was less than 3% for all points.

mal were fit by a power function of the form $y = a(t)^b$. Regression analysis assessed the fit to the measured data.

In vivo *IUdR radiosensitization*

Twenty mice had implantation of the flank xenograft or contralateral subcutaneous control flank with polymers having 0% (empty control) or 50% IUdR on experimental Day 0. For the *in vivo* external beam treatments, the dose (Gy) to the tumor xenografts was first calibrated using radiochromic dye medium (Gafchromic™) mounted in polystyrene mouse phantoms. The change in optical density vs. dose was measured as described by Mayer et al. [39]. Five days after implantation of polymer discs, the animals were restrained in ventilated 50 ml plastic centrifuge tubes with the flank tumors mounted a fixed distance from the collimated 137-Cs source of a laboratory irradiator (Mark I irradiator, Model 68, J.L. Shepard and Associates, San Fernando, CA) as previously described [40]. The external beam radiation regimen was 5 Gy × 2 consecutive daily fractions.

Tumor volumetrics

Measurements of tumor length (L), width (W), and height (H) were made every 3 days. The product ($L \times W \times H$) is proportionate to tumor volume (V). The logarithm of the ratio of this product (V) to the initial product (V_0) (on Day 0 (the day radiation commenced)) for each animal and for the average of each treatment group was plotted versus time. Experimental animals were observed for up to 40 days. For treatment groups showing tumor regression (average $V/V_0 < 1$) the growth delay to return to the original ($V/V_0 = 1$); $\log V/V_0 = 0$) average vol-

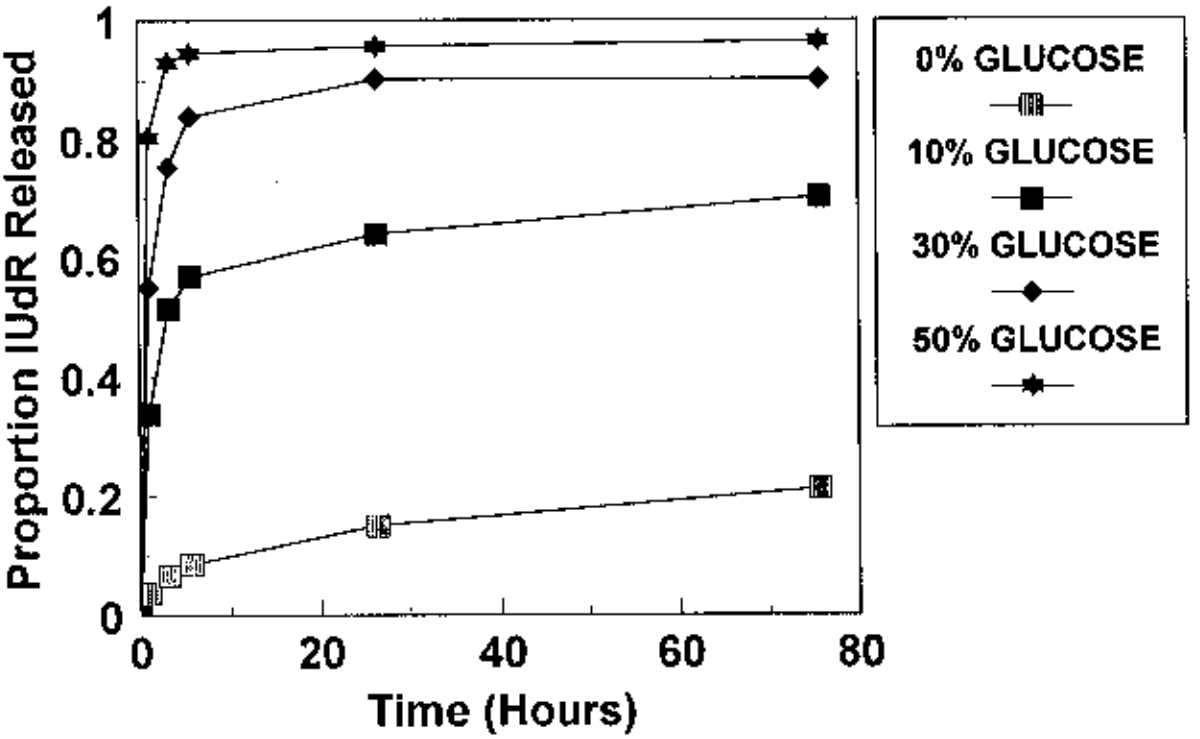

Figure 3. In vitro release profiles of PCPP : SA (20 : 80) polymer discs (10 mg) loaded with D-glucose 10, 30, and 50% by weight and tracer molar amount (20 μCi) 125-IUdR. *Ordinate*: cumulative 125-IUdR released as a percentage of the total activity (μCi) initially loaded into the polymer. *Points*: mean of 3 measurements. The SEM was less than 3% for all points.

ume was measured. For treatment groups having no regression the growth delay to 4 times the original ($V/V_0 = 4$; $\log V/V_0 = 0.6$) volume was measured.

Statistical evaluation

The data are the mean ± standard error of the mean (SEM). Outcomes among experimental groups were compared using Student's t test or analysis of variance [41].

Results

In vitro

IUdR radiosensitization

Without radiation the average plating efficiencies (percent) were 47 ± 1.1 and 24 ± 1.0 for media containing 0 or 10 mM IUdR, respectively. Without IUdR the survival of U251 cells after radiation (Figure 1) was high and was similar to the observations of others [42, 43]. The 10 μM IUdR exposure and increasing radiation doses caused increased cell killing compared to radiation alone. Cell survival ($\log_{10}$) without (control) or with 10 μM IUdR exposures was – 0.12 ± 0.02 or – 0.44 ± 0.05 ($p < 0.001$) for 2.5 Gy, – 0.65 ± 0.03 or – 0.95 ± 0.05 ($p < 0.001$) for 5.0 Gy, and – 1.69 ± 0.02 or – 3.07 ± 0.11 ($p < 0.001$) for the 10 Gy treatment, respectively.

IUdR release

The cumulative percentages of IUdR that were released from the polymers are shown in Figure 2. The early rates of release were high for all loadings of IUdR. The percentages of the loaded IUdR that were eventually released were proportionate to the percentage loading. After 1 day the average cumulative percentage of loaded IUdR released from the

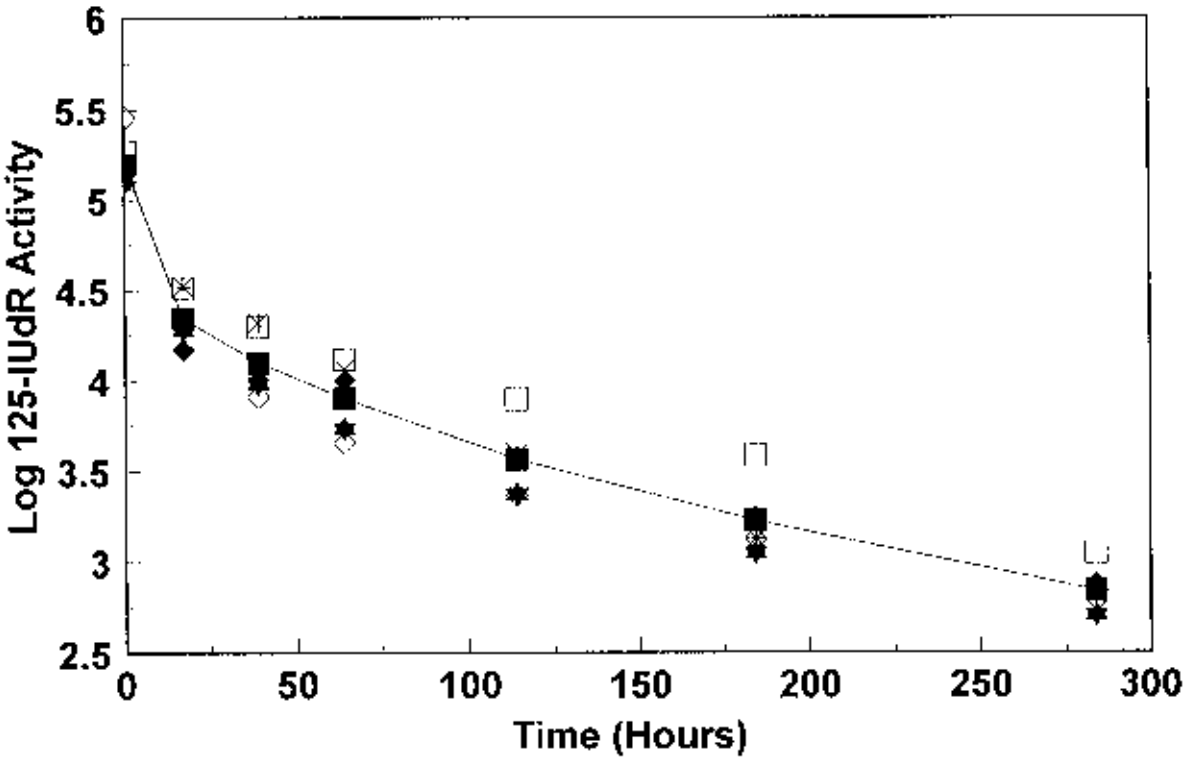

Figure 4. Release of 125-I radiolabeled IUdR from PCPP : SA (20 : 80) polymers implanted in U251 xenografts. Five mice had implantation of U251 flank xenografts with polymer discs bearing 125-IUdR (ca. 200 μCi). Using a collimated scintillation counter, the activity (cpm) in the flanks bearing tumors and polymers was recorded. *Ordinate*: Log_{10} cpm. *Points*: activity vs. time for 5 animals. *Line*: The solid line joining the solid squares represents the mean of the 5 animals. The SEM did not exceed 3% for all points.

polymers having the lowest (10%) loading (34.7 ± 0.4) was less than that released from the polymers having the higher loadings: 51.4 ± 0.7 and 53.3 ± 0.7 ($p < 0.001$ ANOVA vs. 10% loading) for the 30% and 50% loadings, respectively. After 4 days the cumulative percentages were 43.7 ± 0.1, 70.0 ± 0.2, and 90.2 ± 0.2 ($p = < 0.001$ ANOVA) for the 10, 30, and 50% loadings. The percentage IUdR released vs. time was fit to the power function of the form $y = a(t)^b$ where *y* is the cumulative released IUdR, *a* and *b* are constants, and *t* is time (h). Values for *a, b* (R^2) (correlation coefficient) were 32.3, 0.24 (0.94) ($p < 0.00001$ ANOVA) for 10%; 43.0, 0.33 (0.92) ($p = 0.0003$) for 30%; and 44.6, 0.45 (0.94) ($p = 0.0002$) for 50% loadings of IUdR.

125-IUdR polymer release kinetics

Co-loading increasing percentages of D-glucose and fixed activities of 125-IUdR in the polymers caused increased release of 125-IUdR into the media (Figure 3). After 1 h the percentages were 3.7 ± 0.001, 33.9 ± 5.2, 60.8 ± 2.9, and 80.3 ± 1.3 ($p < 0.001$ ANOVA) for the 0, 10, 30, and 50% loadings of D-glucose, respectively. These differences increased with time. After 75 h 21.2 ± 0.01, 70.2 ± 6.6, 89.7 ± 1.2, and 96.6 ± 1.4 ($p < 0.001$ ANOVA) percentages of release were observed for the 0, 10, 30, and 50% D-glucose loadings, respectively. The percentage of 125-IUdR released vs. time for each loading of D-glucose was fit to the power function of the form $y = a(t)^b$. Values for *a, b* (R^2) were 0.03, 0.40 (0.99) ($p = 0.0005$ ANOVA) for 0%; 0.39, 0.15, (0.84) ($p = 0.03$) for 10%; 0.62, 0.11 (0.80) ($p = 0.049$) for 30%; and 0.85, 0.04 (0.71) ($p = 0.11$) for 50% D-glucose loadings, respectively.

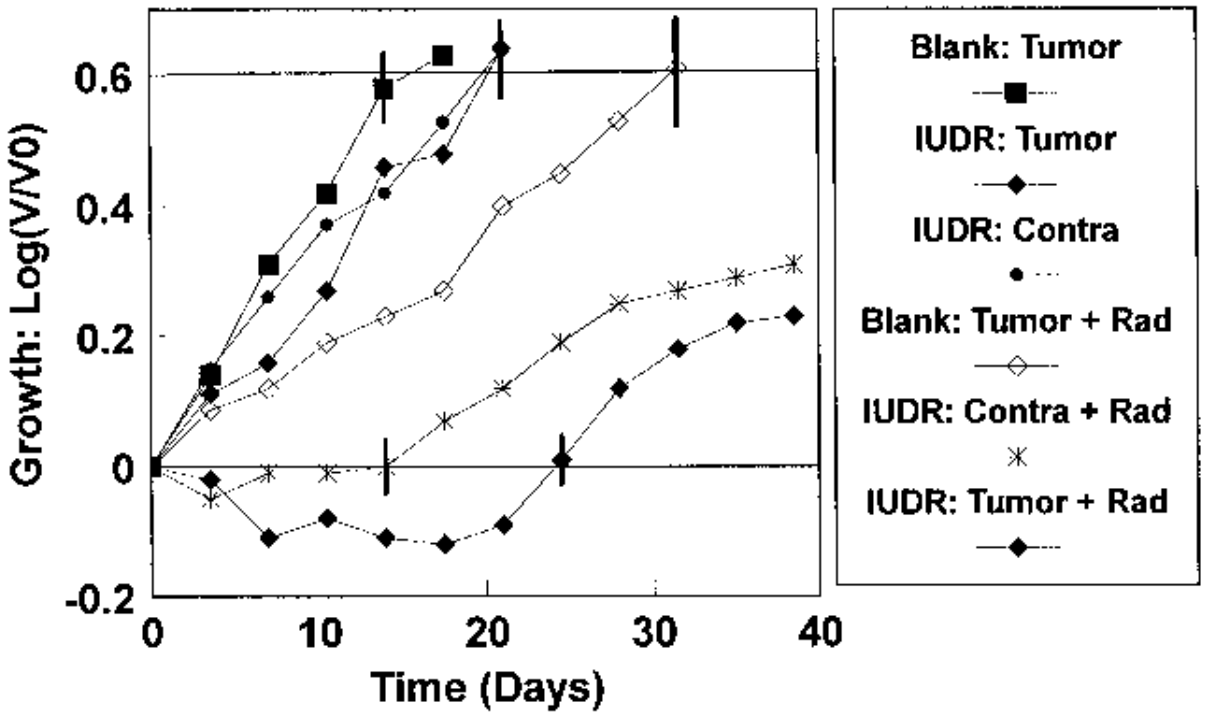

Figure 5. Radiosensitization of U251 xenografts by IUdR polymers. Mice having flank U251 malignant glioma xenografts were treated on Day 0 with an intratumoral or contralateral subcutaneous implant consisting of a 10 mg disc of PCPP : SA (20 : 80) loaded with 0% (empty) or 50% IUdR by weight. After 5 days the xenografts or contralateral flanks had fractionated external beam radiotherapy, 5 Gy administered × 2 consecutive daily fractions. *Ordinate*: Log_{10} V/V_0: Logarithm of the ratio of observed vs. initial tumor volumes for each experimental group. *Points*: Mean ± SEM.

In vivo

125-IUdR polymer release kinetics

The plot of measured activity over the flank xenografts having 125-IUdR polymers is shown in Figure 4. Similar to the *in vitro* release, the initial rates of 125-IUdR release were high but decreased with time. The average activity (log_{10} cpm ± SEM (time (h) after implant)) was 5.2 ± 0.05 (0.5), 4.3 ± 0.07 (17), 3.9 ± 0.08 (64), and 2.8 ± 0.06 (284) ($p < 0.001$ ANOVA). These data were fit to the power function of the form $y = a(t)^b$. For the five flank 125-IUdR polymers the average values for *a* (EN 10^{-5}) and *b* were 1.42 ± 0.06 and – 0.80 ± 0.1 ($p = 0.0007$ ANOVA), respectively. Regression analyses of the fit to the power function showed correlation coefficients (R^2) of 0.85, 0.87, 0.82, 0.95, and 0.73 for the five flank 125-IUdR polymers.

IUdR polymer flank xenograft growth delay

Xenografts having empty polymers grew four-fold in 15.4 ± 1.8 days (Figure 5). Xenografts having IUdR polymers either ipsilateral or contralateral to the tumor and without radiation grew four-fold in 20.1 ± 0.1 or 20.3 ± 3.6 ($p = 0.488$ one-way ANOVA all non-irradiated treatment groups) days. Tumors having empty polymers and radiation had average growth delays of 31.1 ± 2.1 ($p = 0.046$ one-way ANOVA vs. the three polymer treatments without radiation). The two treatment groups having radiation and IUdR polymers contralateral vs. ipsilateral to the tumor showed regression ($V/V_0 < 1$) of the average volumes and required 14.0 ± 3.6 vs. 24.2 ± 0.2 ($p < 0.01$) days to return to their average pre-treatment volumes.

Discussion

In vitro

IUdR radiosensitization

U251 cell killing increased with the dose (Gy) of radiation and was highest after the combined exposures to IUdR and radiation. These results confirmed the radiosensitization of the U251 cell line by a halogenated pyrimidine [44] and provided the basis for the subsequent *in vivo* studies.

IUdR polymer release kinetics: in vitro

The initial rates of release were high for all loadings of IUdR. The PCPP : SA polymer degrades by surface rather than bulk erosion [45]. Such erosion of polyanhydride polymers occurs because of the hydrolysis of the water-labile anhydride linkages [46]. Drugs near the surface of PCPP : SA polymers may thus dissolve and appear very rapidly in the supernatant [47]. This high initial rate of release may subserve loading of drug in anticipation of subsequent protracted and continuously decreasing rates of release.

In addition to the rate, the duration of the continuous release of IUdR is critical for radiosensitization. Halogenated pyrimidines sensitize tumor cells in proportion to the magnitude of their substitution for thymidine in replicating DNA. High percentages of such substitution require exposure during multiple cellular divisions. Depending upon the percentage loading, the *in vitro* results confirmed controlled, protracted release of IUdR over a period of 5 to 10 days. In studies of the continuous systemic infusion of BUdR in mice bearing D-54 human malignant glioma xenografts, equilibrium of thymidine replacement was observed after 7 days [48]. Thus, the duration of release of IUdR by the PCPP : SA polymers corresponds to the interval required for saturation of the replacement of thymidine in growing human malignant glioma xenografts.

A single monoexponential function uniquely characterized the continuous rates of release for each percentage loading of IUdR in polymers. Compared to other drugs for cancer treatment, the controlled, protracted release of IUdR by polymers is particularly important. The characterization of such controlled release in a single expression potentially reflects the rate of a single chemical process: hydrolysis of anhydride bonds in the polymer. Increases in loadings of the hydrophilic IUdR may increase the rate of entry of water into the polymer and result in the increase of the exponential component of the power function.

Co-loading the IUdR polymers with D-glucose caused striking increases in the cumulative amounts of released IUdR. Glucose is hydrophilic and may therefore increase the rate of polymer hydration and degradation [49]. Such co-loading may be an additional means for optimization of the release and delivery of IUdR. For rapidly cycling cells, for example, initially high rates of IUdR release could result in higher rates of thymidine replacement and radiosensitization. Combinations of polymers having disparate loadings of glucose but constant loadings of IUdR could together provide a continuous, high rate of IUdR release for radiosensitization.

In vivo

IUdR polymer release kinetics

The external scintillation counter facilitated observation of the release of activity from the polymer. The observed rate of decrease in activity over the polymer represents the upper limit of the effective half-life. Both intact 125-IUdR and its labeled metabolites were detected. Regardless of the proportions (125-IUdR vs. labeled metabolites), loss of activity with respect to time means regional decrease of 125-IUdR. Determination of the proportion of either intact drug or its metabolites either remaining in, or traversing through the tumor requires further investigation. Additionally, since it is the IUdR which is actually incorporated into DNA rather than that circulating through or near the tumor that causes radiosensitization, these data are mainly important to show the upper limit for retention of IUdR in tumors in this system.

The kinetics of 131-IUdR clearance from the blood and the subsequent appearance of radiolabeled metabolites in plasma after single intravenous injections have been evaluated in rats [50].

The half-life of parent-labeled IUdR was less than 10 minutes, and more than 80% of the total radioactivity was free iodide 20 minutes after injection. Therefore, when compared to single intravenous administrations, the current data suggest that the polymer devices may facilitate comparatively more prolonged, controlled delivery of IUdR.

Radiosensitization

The small growth delay caused by IUdR polymer alone is consistent with the *in vitro* results. In high concentrations IUdR is cytotoxic and causes diminished plating efficiency in U251 cells. Minimal growth delay after IUdR polymer placement alone in the contralateral flank suggests delivery of the drug to the tumor via the bloodstream. The modest growth delay caused by radiation alone is consistent with prior observations in this system [51].

Implantation of IUdR polymer in the contralateral flank followed by irradiation of the tumor caused growth delay. These results suggest delivery of IUdR to the tumor via the blood with resultant radiosensitization. The largest growth delay, however, was observed after placement of the IUdR polymers in the tumors followed by radiation. These results suggest the importance of both local diffusion and delivery via the bloodstream. The proportion of drug delivered by local diffusion vs. circulation in the blood is not known. If the proportion first entering the blood is large and if the rates of peripheral degradation are high, the amount of drug available to the tumor will be low. Conversely, delivery mainly by local diffusion could result in higher bioavailability. The longer growth delay following placement of polymer in the tumor suggests that in addition to delivery via the blood, local diffusion is important.

Conclusions

These results show that a synthetic, implantable, biodegradable polymer allows controlled, sustained release of IUdR both *in vitro* and *in vivo*. The rate of release may be modulated by altering the percentage loading of IUdR or co-loading of D-glucose. The rate and duration of release of IUdR from the polymer is sufficient to radiosensitize human glioma xenografts *in vivo*. This technique holds promise for clinical radiosensitization of human gliomas and other tumors using IUdR and other radiosensitizers.

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