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ABSTRACT

Systemic application of radiolabeled and/or cytotoxic agents should in principle allow targeting of primary and metastatic neoplasms on a cellular level. In fact, drug uptake in non-target but competing cell pools often exceeds toxic levels before sufficient amounts are delivered to tumor. In addition, specific metabolic pathways generally have a low capacity so that at the large concentration of molecules necessary for therapy, effects of saturation are often found. Application of NCT can circumvent problems associated with high uptake in competing non-target cell pools, as the $^{10}B(n,\alpha)^{7}Li$ reaction is activated only within the radiation field. A comparison of this technique with other modes of particle therapy has indicated that NCT provides significant advantages (ref. 1). A major problem still remains in that it is difficult to obtain vehicles for boron transport which demonstrate both the tumor specificity and concentration requisite for NCT. A number of biomolecules have been investigated which show both the necessary concentration and specificity. These include chlorpromazine, thiouracil, porphyrins, amino acids, and nucleosides. Borated analogs of all the above have been described in the literature. In general, however, these analogs have yet to be made available for NCT. Dosimetric implications of binding sites (intranuclear, cytoplasmic, extracellular) are considered, as well as alternate neutron sources. Work performed under Contract No. DE-AC-02-7^{c}CH00016 with the U.S. Department of Energy.

THE "SECOND GENERATION" COMPOUND $Na_2B_{12}H_{11}SH$*

The consensus is that three major problems contributed to poor results in initial clinical trials of NCT; these were: 1) high blood-boron concentration, 2) poor neutron penetration, and 3) excessive dose to surface tissues (ref. 2). Improvements have been made following cessation of NCT in the U.S. The ratio of ^{10}B in tumor to that in blood (^{10}B ratio) is $\sim$1-2 with $Na_2B_{12}H_{11}SH$, vs 0.5 to 0.8 obtained with first generation compounds (ref. 2-4). Also, improved depth-flux distributions have been achieved through the use of an epithermal neutron beam which uses tissue as a moderator to generate thermal neutrons at depth (ref. 5). Clinical trials of NCT have been in progress since 1968 in Japan under the direction of Dr. H. Hatanaka. To date approximately 45 patients have been treated with $Na_2B_{12}H_{11}SH$ and a thermal neutron beam. There are some apparent 8-9 year "cures," and on the average, an extension of average survival by a factor of approximately 3 (ref. 6).

*Available from the Callery Chemical Co., Callery, PA, 16024.

NEW COMPOUNDS: CHLORPROMAZINE, THIOURACIL, PORPHYRINS, AMINO ACIDS, NUCLEOSIDES, ANTIBODIES, AND STEROIDS

The full potential of NCT should be achieved with "3rd generation" boron compounds showing binding to tumor and clearance from normal tissues.

Chlorpromazine (CPZ): Studies with CPZ in animal models of melanoma have shown that the biological half-life is ~10 days, that tumor/tissue concentration ratios vary from ~15 to 100 and that concentrations are adequate for therapy* (ref. 7). Studies in Japan with the borated analog have demonstrated tumor regression with tumor models in hamsters, physiological binding and enhanced response to neutrons in single cell cultures, and successful application against spontaneous melanoma in swine (ref. 8-10). Synthesis of the borated analog is described by Nakagawa (ref. 11).

Thiouracil (TU): Thiouracil is thought to be a false precursor in the biosynthetic pathway of melanin. Studies have demonstrated a biological half-life in the order of days, and a concentration in tumor 100 times greater than that in other tissues. Concentrations adequate for therapy have been easily obtained (ref. 12). A borated analog of uracil has been described by Schinazi (ref. 13).

Porphyrins (TPPS): The substitution of carboranes in place of the 4 phenyl rings in tetraphenylporphinesulfonate (TPPS) as described by Haushalter (ref. 14) produces a relatively large molecule which is 58% by weight boron. Since all tumors appear to take up TPPS, its applicability would in principle be universal, while that of CPZ or TU is restricted to melanoma. Distributions of TPPS which we have measured in 6 different tumor models are more than adequate for therapy (ref. 26).

Amino Acids: Initial studies with ^{14}C labeled glycine in our murine melanoma reveal a tumor/brain ratio of ~10, a tumor/blood ratio of ~5, and concentrations adequate for therapy. Following a synthesis similar to that described by Spielvogel (ref. 15), a borated analog of glycine (H_3NBH_2COOH) has been produced by the Callery Chemical Co. Exploratory experiments indicate that the latter compound does not show uptake in tumor analogous to that of glycine. Efforts are under way in collaboration with Dr. Spielvogel and also with the Callery Chemical Co. to develop improved compounds.

A borated analog of phenylalanine has been reported by Mishima which has provided marked radiation enhancement in tissue culture (ref. 16), and uptake in melanoma (via incorporation in the biosynthetic pathway of melanin) adequate for therapy (ref. 10).

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*It is assumed throughout that a concentration of ~35 µg boron-10/gram tumor is adequate for therapy.

Nucleosides: A borated analog of thymidine has been described by Schinazi (ref. 13). If 3.2×10^9 thymine bases are available for substitution per 100 μ^3 nucleus (ref. 17), it follows that at 5% replacement (average or bifilar), the nuclear boron concentration would be 25 μg B/g, which should be more than adequate for therapy. Five % replacement of Tyd has been reported *in vivo* in human tumors (ref. 17). Replacements of Tyd with IdUrd in excess of 10% have been obtained in murine melanomas (ref. 18). A rather extensive analysis has indicated that it should be possible to treat brain tumors with analogs of Tyd, as tissues of CNS do not synthesize DNA (ref. 17).

Antibodies: A number of groups have developed procedures for borating antibodies (ref. 19-21). In particular, Sneath et al. have been able to attach 1100 boron atoms per IgG molecule (ref. 21). However, it yet remains to be demonstrated that antibody specificity and activity remains adequate for NCT.

Steroids: A number of reports have described the synthesis of borated steroids for possible use for NCT (ref. 22, 23). To date however, it is not clear whether receptor site concentrations will be high enough to allow boron accumulations adequate for NCT.

DOSE DISTRIBUTIONS, DOSE MODIFYING FACTORS, AND ADVANTAGE FACTORS

Dose distributions in tissue are shown for a thermal and an epithermal beam, as a function of depth in Table 1 (ref. 5). The high dose rates are typical of the intense beams employed when boron concentrations were transitory, and it was thought necessary to deliver therapeutic doses in a few minutes.

The absorbed dose rates given in Table 1 can be used to evaluate physical dose. Biological response will be modified by the Relative Biological Effect (RBE) of each radiation component, and also by the cellular distribution of ^{10}B. These parameters are listed in Table 2. Survival curves for various cellular distributions of ^{10}B were calculated by Kobayashi and Kanda (ref. 25), assuming 20 μg ^{10}B/g tissue, spherical cells and cell nuclei (radii of 5 and 2.5μ respectively), and a close-packed structure with nearest neighbors 10μ apart. Response was based on calculated absorbed dose to the nucleus; the relative efficacy of each distribution was obtained from the ratio of D_o's. Thus we see that concentrations of boron in the cytoplasm (as would be obtained with CPZ and TU) may have to be twice as high as that for a uniform distribution for successful NCT, while for an extracellular distribution (as may be appropriate for antibodies) concentrations would have to be almost 4 times as high.

The ratio of tumor dose to the maximum dose delivered to normal tissues represents the "advantage factor." Advantage factors have been calculated for a thermal and an epithermal beam from absorbed dose distributions in Table 1, assuming a boron concentration in tumor of 35 and 70 μg/g. Thirty five μg ^{10}B is generally considered to be the minimum usable for NCT, and serves as a use-

ful reference point. The increased therapeutic gain produced by the deeper penetration of epithermal neutrons for depths greater than ~1.5 cm is significant. Also, the benefit obtained as boron clears blood and normal tissue is large (^{10}B ratio $\geq$ 10). Advantage factors for any combination of parameters can be derived from data presented in Tables 1 and 2. Increased values are of course obtained when the RBE of 3.7 for the $^{10}B(n,\alpha)^{7}Li$ reaction is incorporated.

TABLE 1

Absorbed dose rate (rads/minute) in a tissue equivalent anthropomorphic phantom.*

Depth in tissue	Thermal neutron beam				Epithermal neutron beam			
cm	γ	N	H	^{10}B (35 μg/g)	γ	N	H	^{10}B (35 μg/g)
0	530	205	90	2925	50	3	183	42
1	530	150	70	2140	78	10	144	130
2	490	110	50	1500	88	13	111	193
3	415	75	40	1030	93	14	85	212
4	350	50	30	670	93	14	64	201
5	285	30	20	460	88	12	49	180
6	225	20	17	300	81	10	40	151
7	180	10	15	190	73	8	32	121
8	145	7	12	130	66	7	27	95
9	115	5	10	70	59	5	22	75
10	95	3	8	50	53	4	20	60

*Medical Research Reactor, Brookhaven National Lab; reactor power 5 Mw (ref. 5). γ, N and H = dose from $H(n,\gamma)D$, $^{14}N(n,p)^{14}C$, and proton recoils.

TABLE 2

Dose modifying factors.

Relative Biological Effect		Cellular ^{10}B Distribution	
Radiation	RBE*	^{10}B location	D_o/D_o (uniform distribution)†
Gamma (γ)	1	uniform	1.0
$^{14}N(n,p)^{14}C$	2	nucleus + cytoplasm	1.2
Proton recoil (H)	2	nucleus	2.0
$^{10}B(n,\alpha)Li$	3.7	cytoplasm	2.1
		extracellular	3.8

*from ref. 24
†from ref. 25

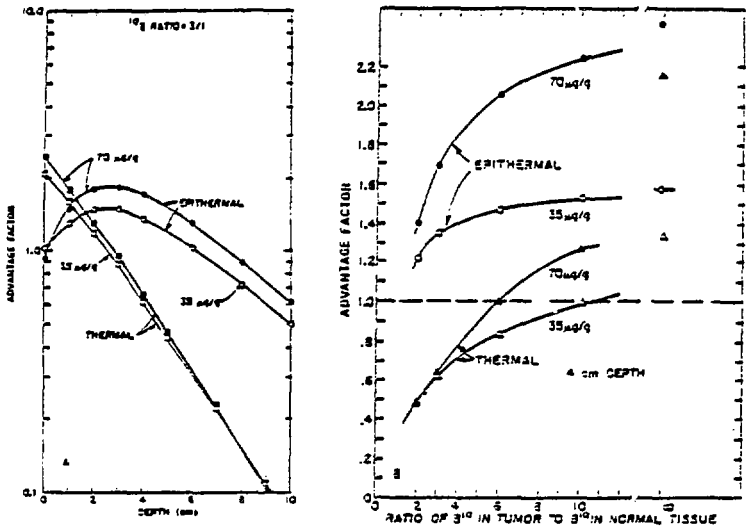

Fig. 1. Advantage factors (ratio of tumor dose to maximum normal tissue dose) as a function of depth in an anthropomorphic phantom for a ^{10}B ratio (tumor/normal tissue concentration ratio) of 3/1 (Fig. 1A). The same is shown in Fig. 1B at 4 cm depth, for various ^{10}B ratios. Results for tumor boron concentrations of 70 and 35 μg/g tumor are illustrated.

DISCUSSION AND SUMMARY

The important characteristic common to the "new compounds" described above is that they show physiological binding to tumors, so that the effective half-lives for retention in tissues is in the order of days. This then relaxes the requirement for intense neutron beams, as dose can then be delivered in a series of "fractionated" exposures. The possibility of utilizing lower intensity neutron sources may permit the use of neutron beams with significantly improved physical characteristics, as may be obtained with a scandium filtered (2 keV) neutron beam (ref. 2). Depth-flux-density curves from such a source should show better penetration than the epithermal beam in Table 1, and in addition should have a much lower fast neutron contamination. Other lower intensity neutron sources may also then become useful for NCT. These would include Cf-252, portable (α,n) sources, D-T and D-D generators, as well as spallation (p, Pb) sources. Further gain may be obtained as normal tissues repair low LET damage during protracted irradiations.

Seven classes of biomolecules are described above which show physiological targeting to tumors suitable for NCT. Borated analogs of these compounds have been described in the literature. Yet with a few exceptions, little effort is being directed towards the synthesis of these compounds within the U.S. The physical and radiobiological benefits to be gained from an effective vehicle for boron transport to tumor are substantial. It is hoped that support can be generated for the synthesis of such compounds for testing in NCT.

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