DOWNLOAD PDF REACTIONS TOWARD THE SYNTHESIS OF MINOR-GROOVE BINDING HYPOXIC CELL SENSITIZERS

Chapter 1 : Radiosensitization by Reaction with DNA Radicals - Antimicrob Agents

Mitomycin C linked to DNA minor groove binding agents: synthesis, reductive activation, DNA binding and cross-linking properties and in vitro antitumor activity Manuel M Paz, Arunangshu Das, Maria Tomasz.

A recognition of the medical health profession to the lack of efficacy of radiation on certain tumors has arisen. Specifically, species of tumors exist wherein due to rapid growth rate or other characteristics, an oxygen depleted or hypoxic zone exists within the tumor. Such hypoxic cells are not amenable to traditional radiation therapy without incurring such severe conditions so as to endanger healthy tissues. To overcome this lack of efficacy in radiation therapy various means for administering oxygen to hypoxic tumors has been described in the prior art. McIntosh in Transfusion Medicine: Recent Technological Advances, page 29 through 38, demonstrated the use of Fluosol-DA to enhance the effect of radiation on animal tumors. The treated animals are then subjected to photon radiation after the intravenous injection. The author found that the presence of the fluorochemical did enhance the effect of radiation therapy. No work accompanied the proposal to demonstrate the overall effect of such a proposal. Biology and Physics, volume The patent mentions intramuscular administration or injection at or near the site of hypoxia but teaches away from this by reciting that "direct contact" is ideal but "may not be achievable and in fact is not required. Biology, and Physics, volume 12, pages to , the treatment of mice with a Fluosol-DA emulsion to heighten favorable response of radiation therapy on mammary tumors. The test mice did not show favorable enhancement when breathing air or nitrogen or when breathing carbogen alone without Fluosol emulsion injected intravenously. Only when Fluosol emulsion was injected intravenously while the mice breathed a carbogen-containing atmosphere did enhanced radio therapy efficacy become observed. In light of the oxygen-enriched breathing the McIntosh therapy necessarily involves vascular circulation of the emulsion to the lungs. Radiation or chemotherapy is then administered to the patient after the emulsion has carried oxygen from the lungs to the vicinity of the tumor. All of the above described procedures utilize injections that require circulation through the lungs or vascular system in order to carry oxygen to the tumor and therefore to enhance radiation therapy effects. Preferably the radiation treatment is performed promptly after administration of the emulsion. Preferably, the fluorocarbon is oxygen saturated and is selected from the perfluorocarbon group consisting of perfluoroperhydrophenanthrene perfluoro n-butyldecalin and mixtures thereof. Preferably the emulsion comprises a perfluorocarbon with a vapor pressure less than 5 torr. Preferably the radiation comprises x-rays in the dose of above approximately and up to 5, rads administered up to 15 minutes after the administration of the emulsion. Alternatively, the method can be performed in a series of emulsion administrations, each followed by radiation treatment or an emulsion administration followed by a series of radiation treatments over a period of time. Preferably the perfluorochemical emulsion is administered in an amount no greater than 0. In addition, localized thermal treatment has been used to induce more oxygen at the site of the tumor cells. Both methods have been applied clinically. Such techniques have arisen from the problem in treatment of many mammalian tumors which have necrotic zones that strongly suggests the presence of hypoxic cells, which when presented with molecular oxygen revert to radio sensitive cells and consequently become targets for radiation treatment that destroys them. No direct method of supplying molecular oxygen to such hypoxic cells has been demonstrated to date prior to the present invention. The tumors are immediately up to 15 minutes irradiated with to 2, rads of radiation 10 to 30 Gy of NeV photons. The solublized oxygen oxygenates the hypoxic tumor cells and acts as a adjuvant for photon radiation therapy for more effective radiation cell kill. Therefore, the present invention provides oxygen readily for radiation therapy, which in intravascular applications of the prior art can not supply sufficient oxygen for the same level of effect for radiation treatment. The present invention, in effect, allows for a more rapid and direct transfer of soluble oxygen to the centers of radio resistant hypoxic tumors cells than the intravascular means or thermal excitation of the prior art. The theory as to why the present invention provides an efficacious therapy treatment of improved degree

over traditional intravenous therapies is based upon the proposed understanding of the activity of oxygen and radiation. Ionizing radiation has been used in the treatment of cancer and tumors for over 80 years. Photon radiation can cause cell destruction by indirect interaction through the formation of chemically reactive free radicals. For this to occur, oxygen must be present. Short lived free radicals are formed when both radiation and oxygen are present in tissue. These free radicals interact with the intracellular nucleic acid molecules DNA, RNA causing damage which will lead to cell death. Oxygen must be present at the precise moment of radiation therapy. If a tumor grows rapidly enough, it will outstrip its vascular supply thereby reducing the amount of oxygen to its cells. When the cells have less oxygen to sustain normal metabolism, they become oxydeficient or hypoxic. If the oxygen deficiency becomes too great, then these cells will die, forming necrotic zones. These hypoxic cell populations found in rapidly growing mammalian tumors around necrotic zones are radiation resistant. They do not respond as well to radiation induced cell kill as normal fully oxygenated cells. Such hypoxic cells require fold increase in the radiation dose to achieve similar cell death as normal oxygenated tumor cells. In light of this problem, the present invention provides a therapeutic approach by which oxygen can be made readily available to the immediate area of hypoxic tumor cells to provide the necessary oxygen content for effective radiation therapy, resulting in the destruction of such cells. The present invention utilizes a method for the direct administration, i. This differs from the intravenous administration of the prior art. Such direct interstitial administration of the oxygenated emulsion provides an unexpected effect on the reduction of tumor growth by increasing tumor doubling time. In order to qualify as an appropriate fluorochemical emulsion or microemulsion, emulsions used in the present invention must be biocompatible with normal tissue and cells. An emulsion pH of 6. The emulsion particle size may range from 0. Particles of larger size greater than 0. Preparation of the emulsion may be performed by homogenization, sonication, ultra-mixing, microfluidization or spontaneous mixing as in microemulsions. The preferred method of formation of the emulsion is microfluidization because more absolute control of the particle size is achievable with a minimum of energy input per unit volume of emulsion prepared. The fluorochemical emulsion administration dosage is preferably in the range of 0. The fluorocarbon should have a vapor pressure of less than 5 torr. It is preferred that the fluorochemical have vapor pressure of less than 1 torr. The ideal fluorochemical is a fully fluorinated condensed C14 material, such as perfluoroperhydrophenanthrene or partially condensed perfluoro C-4, C-5, C-6 alkyldecalins, such as perfluoro n-butyl decalin. The fluorochemical emulsion used in the method of the present invention requires a surfactant to emulsify the fluorochemical in an aqueous phase. The fluorocarbon mixture itself has the following physical chemical properties reported in Table I. The lecithin mg was initially dissolved in 2 to 3 milliliters of chloroform which was evaporated off using nitrogen or argon in order to coat the sides of the glass test tube. Finally, the emulsion was sonicated at high energy three times for six to eight seconds, allowing at least one minute between sonications. Particle size measurements were made on a Nicomp laser light scattering device and determined to be 0. This emulsion was used in the experiments demonstrating the subject invention below. The tumor was grown in the hind flank of each animal. Tumors were allowed to grow for 21 days prior to radiation or injection of test substances. Tumors were passaged by seeding each animal with either a small piece of tumor obtained from a previously grown tumor or by injecting tumor cells harvested from tissue culture. All tumors were injected subcutaneously into the right hind flank of each animal using sterile procedures. Tumor growth volumes were determined daily. The length 1 , width w , and depth d of the tumor was measured using a vernier caliper, and the volume of the tumor was calculated assuming that the tumor shape approximated that of ellipsoid according to the following formula: Assuming simple exponential growth, a least square analysis of the natural log of the tumor volumes versus days was calculated using a computer program. The animals were anesthetized during the radiation procedure. Only the tumor in the flank was irradiated through use of a specially constructed jig which allowed placement of the tumor directly into the radiation beam. The animals were administered 10 MeV photons from a Clinac 18 Therapy machine. After radiation, the tumor volumes were determined daily post radiation. These results are shown in FIG. Using the

same analysis of the tumor growth data, it was determined that rads had no effect on tumor doubling time. Increasing the radiation dose to rads, resulted in a marginal decrease in the growth rate increase in doubling time was demonstrated , while at rads, a significant therapeutic reduction in the growth rate from the average doubling time increasing to 6. As a result of these tests, it was decided to administer a radiation dose of at least rads to the tumor, while evaluating the effectiveness of oxygenation using interstitial direct injection of the oxygenated fluoro chemical emulsion into the hypoxic zone of the respective tumors. It is possible to administer a radiation dose up to rads. Within five to ten minutes after injection of the solution, the tumors were irradiated with rads 25 Gy of 10 MeV photons. The results of this radiation control are shown in FIG. Finally, the experimental demonstration of the subject invention consisted of injecting interstitially the fully oxygenated fluoro chemical emulsion directly into the tumors of similarly treated hamsters. Procedures and methods were identical to those described above. Tumor growth was measured as previously described. The results of the subject invention are also shown in FIG. The average tumor doubling time increased to Table 2 summarizes the results of the control and subject invention experimental confirmation studies. In addition, the mean survival time was also determined for each group of animals. The survival time is defined as the length of time it takes an animal to die from the tumor after initial seeding. In some instances the animals would cannablize the tumors, and therefore, some of these animals were removed and counted as dead. The mean survival times for the animals was the greatest in animals treated with both the perfluoro chemical emulsion and radiation. The present understanding of these studies is that the fluorochemical emulsion system transports sufficient quantities of oxygen via small micro particles directly to hypoxic regions within the tumor volume, through the extra cellular space. The extra oxygen carried by the emulsion particles equilibrates with regions of low oxygen tension hypoxic cells by diffusion, thereby raising the oxygen tension towards normal or higher levels. These cells revert to normal oxygen metabolism instantly, and therefore are more receptive to cell kill by radiation. The key feature to this invention is the direct interstitial administration of pre-oxygenated perfluoro chemical emulsion into the hypoxic zone of the tumor. This method delivers the greatest amount of oxygen directly to the critical portion of the tumor without dilution from the vascular pool and accordingly reoxygenates the subpopulations of the hypoxic tumor cells for more effective radiation cell kill. This is evident as a significant increased tumor doubling time and greater mean survival over the control test, as described in and identified above. This differs from the prior art which depends on oxygen uptake from the lungs or the blood in the vascular system.

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Nitroimidazoles are being studied extensively as hypoxic cell radiosensitizers. Besides their ability to selectively sensitize hypoxic cells to radiation, which depends on the parent compound, nitroimidazoles have a variety of other effects in vitro, in vivo and clinically which appear to require reductive metabolism.

Contact MedChemComm Novel benzoyl thioureido benzene sulfonamides as high potent and selective inhibitors of carbonic anhydrase IX: In this study, a series of sulfonamides derivatives were designed and synthesized as Among them, derivatives 4a and 4b possess To cite this article before page numbers are assigned, use the DOI form of citation above. Also, these phosphate groups are often cleaved off by phosphatases. Grimsey, Michelle Glass, Joel D. Vernall High affinity, cannabinoid type 2 receptor selective ligand. An easy pathway to camphor based N-acylhydrazones containing in Hoppe This study has identified several compounds with potential for repurposing against Trypanosoma brucei. Synthesis, in vitro cytotoxicity and SAR analysis Med. B has become one of the most significant public health problems in recent years. Antibiotic therapy remains the mainstay of T. B control strategy, but the increasing resistance of mycobacterial Lieberman, Sami Khaznadar, John A. Jacobson Adenines that incorporate known agonist affinity-enhancing substituents are A3AR-selective antagonists. Salakhutdinov Camphor based heterocyclic systems containing 1,3-thiazolidinone and thiazole rings showed promising antiviral activity towards Orthopoxviruses. Luyt A 68Ga-labelled ghrelin analogue is described as a high affinity peptide for ghrelin receptor PET imaging using a sequence derived directly from the endogenous ligand, yet modified for improved stability. C3, in particular, having a ligand derived from benzocaine, exhibited greater selectivity toward HeLa cells, arrested cell cycles, and promoted tumor cell apoptosis. Obianom, Yong Ai Novel hybrids derived from aspirin and chalcones were designed and synthesized. Maguire, Zhi Chen, Vani P. Mocharla, Madhavi Sriram, Tracy E. Pinney Dihydronaphthalene analogues as potent inhibitors of tubulin polymerization, cytotoxic agents, and vascular disrupting agents VDAs. Concepcion, Aaron Joseph L. Villaraza Nobilamide B, a TRPV1 antagonist, and a series of Ala-substituted analogues were synthesized and their neuroactivity was assessed in a primary culture of dorsal root ganglion DRG neurons. In vitro and in vivo evaluation of novel pharmacological tools: Bojarski Close structural analogues of 5-carboxamidotryptamine 5-CT based on the newly discovered indole-imidazole scaffold were synthesized and evaluated to search for a 5-HT7 receptor agonist of higher selectivity.