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Radiosensitizers

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Abstract

Radiosensitizer are the compound, when combined with the radiation, attain greater tumor inactivation and has less effect on the normal tissue, respectively. It is basically a drug that makes tumor cells more sensitive. Radiotherapy is getting great recognition in recent time and nowadays, achieving rapid advancement. This paper aims to review the advancement and the compounds those are used for radiosensitizer also known as radio-enhancer. The evolution of radiosensitizers with probes, like radionuclides and contrast agents which are used for magnetic resonance imaging and computed tomography, has showed great progression in image-guided RT. These radiosensitizers are favorable for therapeutic uses and also for diagnosing and treating tumors. In this review, we highlight recent progress on radiosensitizers. Chemotherapy combined with radiation is used in the adjuvant therapy in maximum cancer patients, and trails have also shown better result rather than radiation alone in the treatment

Keywords *Radiosensitizer, 5-fluorouracil(5FU), Gemcitabine, Nanoparticles, Nitroimidazoles, Ornidazole*

Definition

Radiosensitizers are compounds that, when combined with radiation, achieve greater tumor inactivation than would have been expected from the additive effect of each modality (1). Radiosensitizers are agents that increases injury to tumor tissue by causing damage to DNA and also by releasing free radicals.

Types of Chemical Radiosensitizer:

An early pioneer in this field, G. E. Adams, divided radiosensitizers into five categories [2,3]:

- Suppression of intracellular-SH [thiols] or other endogenous radioprotective substances.
- Radiation-induced formation of cytotoxic substances from the radiolysis of the sensitizer.
- Inhibitors of post-irradiation cellular repair processes.
- Sensitization by structural incorporation of thymine analogues into intracellular DNA.
- Oxygen-mimetic sensitizers, for example the electron affinic drugs

Another leader in this area, E. J. Hall, while discussing radiosensitizers, emphasized on the importance of effect between normal tissue and tumor, suggested that in the fifth edition of his standard text [4] 'only two types of sensitizers have found practical use in clinical radiotherapy:

The halogenated pyrimidines. based on the premise that tumor cells cycle faster and, therefore, incorporate more drugs than the surrounding normal tissues.

Hypoxic cell sensitizers increase the sensitivity of cells deficient in molecular oxygen. based on the premise that hypoxic cells occur only in tumors and not in normal tissues.

Mechanism of Action

The linkage amongst tumor hypoxia and prognosis after the radiotherapy, and also with tumor proliferation, malignant phenotype as well as susceptibility to some chemotherapy regimens, are well established now [5]. According to studies, nicotinamide, the amide form of vitamin B3, comparatively was non-toxic, tumor specific radiosensitizer [6,7]. Mechanisms by conventional chemotherapeutic agents produce radio sensitization is still unknown. The mechanisms of sensitization of some of the most widely used conventional chemotherapeutic sensitizers, the nucleoside analogs. Goal is to identify areas of potential joint research between clinicians and laboratory scientists that would permit to apply these agents more rationally in combination with radiation.[8]

5-fluorouracil(5FU) and Fluorodeoxyuridine: It has been used widely with radiation, and has both DNA and RNA directed effects. Although the disruption of RNA or DNA synthesis can produce cell toxicity, some evidence have also suggested that radio sensitization is due to thymidylate synthase inhibition.[9] the various mechanisms through which 5FU could increase radiation sensitivity at the cellular level are firstly, is by killing of S phase cells, which are comparatively radioresistant.[10] Many hypothesis tells that increased radiation sensitivity takes place in cells that have inappropriate progress through S phase in the presence of drug. Initially it was found that the radio sensitization by fluorodeoxyuridine (FdUrd) appeared in HT29 human colon cancer cells, which started G1/S cyclins in drug presence, but not SW620 cells [11] This conclusion is supported by studies and has shown S phase entry blockage by releasing an arrest in G1. Moreover, SW620 cells show sensitization by FdUrd when transduced with the viral protein (HPV E6)[12]. Viral protein deactivates the retinoblastoma protein, releases S-phase transcription factors and cells driving through S-phase. [13,14] Introduction of oral 5FU forms(prodrug capecitabine) which is now approved in United States makes treatment with radiation and the drug way more easier in the clinics. Capecitabine has capability to interact

differently from protracted venous infusion 5FU based on preclinical studies indicating that radiation can induce thymidine (inhibitor of phosphorylase in tumor cells) [15]. Various efforts have been conducted toward development of assays that will anticipate the response to 5FU as chemotherapeutic agent. High levels of thymidylate synthase shows resistance to treatment [16] as high levels of the 5FU catabolic enzyme dihydropyrimidine dehydrogenase.[17] It shows that these level also helps predicting the ability of 5FU to act as radiation sensitizers, although clinical data are lacking at current time.

Gemcitabine: The gemcitabine activity against a variety of tumors incorporated with evidence that it affected deoxynucleotide triphosphate (dNTP) pools indicated that it might be a radiosensitizer. There was no confirmation of radio sensitization when the cells were irradiated before gemcitabine exposure, although the ratio of improvement was observed when cells were incubated for 24 hours before irradiating. Studies described results by disclosing that maximum sensitization was produced under conditions in which cells were distributed into S-phase and were depleted of phosphorylated deoxynucleotides (mainly dATP). These conditions could produce both by continuous exposure to (10-30 nmol/L) of gemcitabine or 8 to 48 hours after a 2-hour exposure to 100 nmol/L (noncytotoxic) [18]. Further studies have shown that cells obtained from head and neck cancers, breast cancer and adrenal cancers are sensitized by gemcitabine.[19-21]. Evidence shows that inhibition of ribonucleotide reductase is the main step for producing sensitization. Firstly, the time period of dATP pool depletion matches the time course of radio sensitization [17,19]. Secondly, cells which are widely varying endogenous dNTP pools and sensitivity to gemcitabine were sensitized uniformly when similar d ATP pool depletion and S Phase redistribution were made [19].It has also been suggested that radio sensitization of log phase cells takes place by selective sensitization of S-phase cells which are radioresistant[22].The role of DNA repair in gemcitabine-mediated radio sensitization, shown the role of mismatch repair. Experiment was done by using HCT-116 cells containing a mutation in the mismatch repair gene MLH1, and HCT-116 cells transduced with chromosome 3, which showed mismatch repair capabilities. Mismatch repair defective cells were resistant to radio sensitizing effects as well as cytotoxic cells of gemcitabine compared to mismatch repair cells. Recent studies showed cells with genetic defects in repair pathways shows that defects in nonhomologous rejoining have zero effect on radiation sensitivity[23] cells lacking capability to carry out homologous end rejoining reveals higher sensitivity[24] .S phase is known to be important key cell cycle phase associated with increased radiation as nonhomologous end rejoining tends to predominate in G1 cells, and homologous end rejoining might act as the major repairing mechanism for cells in S and G2 phase.

Applications of Radio sensitizers

Nanoparticles as Radiosensitizers: Recent progress have been made towards nanoparticles to propose them as novel radio sensitizers. Nanoparticles (NPs) are defined as particles between 1 and 100 nm.[25] They have more cell penetration and less adverse effects than conventional radio sensitizers.[26] Among nanomaterials which have this radio sensitizing nature, carbon nanotubes,[27] gold nanoparticles (GNPs)[28] and other metallic nanoparticles[29] can be mentioned.

Application of NPs as radio sensitizers is a promising strategy to increase the efficiency of radiotherapy. The assessment of preclinical studies helps to shape further trials. Further, it prevents unnecessary study replication and opens way for successful clinical trials. Thus, we intended to conduct this review with a focus on study methods and results. This is the first review of the literature which assessed the application of NPs in radiotherapy as radiosensitizer.

Nitroimidazoles as radiosensitizers: an extension of studies on the clinical use of nitroimidazoles as radiosensitizers, single-dose pharmacokinetic studies of iv metronidazole (500 mg/100-ml vials) were performed in eight consenting patients. Single doses of 0.5, 1.0, 1.5, and 2.0 g (0.29-1.21 g/m2) were administered iv by a zero-order infusion pump. Serial timed blood and urine samples were assayed for metronidazole and its two metabolites (acetic acid and ethoxy compounds) using a high-pressure liquid chromatographic assay. Open two-compartment kinetic characteristics of metronidazole were computed from simultaneous plasma infusion and urine excretion-rate equations using a nonlinear least-squares regression analysis program (NONLIN). Means of the four kinetic parameters were (h-1): k12, 1.18; k21, 0.86; k10, 0.22; and k'e, 0.46 x 10(-4). Means of the apparent volumes of distribution were (liters/kg): Vc, 0.41; VB, 1.02; and Vss, 0.75. The mean (+/- SD) for alpha-half-life was 1.2 +/- 1.3 hours, and that for beta-half-life was 9.8 +/- 5.9 hours. Seven of the eight patients received a second identical dose orally 1 week later, and the absolute bioavailability was estimated to approximate 100%. Unless the oral route is not feasible and if immediate high peak blood levels are not necessary, oral metronidazole is the preferred route of administration of metronidazole for its radio sensitizing effects [30].

Ornidazole as radiosensitizer: is a hypoxic radiosensitizer, and is a derivative of 2-nitroimidazole intended to reduce neurotoxicity due to its blood brain barrier (BBB) impermeability [31, 32]. Several studies have shown that ornidazole has a radio sensitizing effect under hypoxia, both in vitro[33–35] and in vivo[35–37]. Based on these studies, a phase III trial of ornidazole against advanced pancreatic cancer was performed; it was demonstrated that treatment with ornidazole following radiation

significantly improved the tumor mass reduction rate and extended patient survival [38]. While various results have suggested that ornidazole has promising potential in hypoxia-targeting chemoradiotherapy, to date there have not been any reports on the use of this drug for intracranial glioma.

It is known that the BBB restricts the transport of hydrophilic or high-molecular-weight compounds into the brain to maintain the brain internal milieu. Therefore, ornidazole, which has a hydrophilic residue, cannot cross the BBB and cause any toxicity to the intact brain. However, in many advanced malignant gliomas, disruption of the BBB has been reported [39–41]. These facts led us to consider the possibility that doranidazole might only reach the tumor regions and not the surrounding healthy brain.

Fluorouracil as radiosensitizers: 5-Fluorouracil (FUra) and Fluorodeoxyuridine (FdUrd) are analogues of uracil and deoxyuridine, respectively. Randomized trials have demonstrated local control and survival advantages with systemic FUra and radiation compared with radiation alone in patients with rectal cancer, esophageal cancer, and pancreatic cancer. [42] .FUra and FdUrd, through their metabolites lead to cell cycle redistribution, DNA fragmentation, and cell death. [43] Whereas clinically achievable concentrations of FdUrd produce only DNA-mediated cytotoxic effects, FUra can also kill cells by RNA-dependent mechanisms. [44]

Conclusion

Radiation combined with chemotherapy is used in adjuvant therapy in maximum cancer patients, and trials have also shown better results rather than radiation alone in the treatment. Radiosensitizers are rising agents that enhance injury to tumor tissue by increasing DNA damage and releasing free radicals. Some radiosensitizers are already in clinical use and some are in the preclinical phase. The development of labeled radiosensitizers with probes, have led to great progress in IGRT and are promising for use as radiosensitizers that can be used as therapeutic agents for diagnosing and tumor treatment. Conventional chemotherapeutic agents produce mechanisms of radio sensitization is still unknown and of some of the most widely used conventional chemotherapeutic sensitizers, the nucleoside analogs. Aim is still to identify areas of potential joint research between clinicians and laboratory scientists that would permit to apply these agents more rationally in combination with radiation.[8] In conclusion, there are several new approaches in this field of chemical radiosensitizers that show promise, but their mechanistic basis is researched poorly. As a result, it is expected that

ultimately a radio sensitizing drug would be invented that will overcome the flaws so far encountered in their use in the clinic.

References

1.Leibel and Phillips Textbook of Radiation Oncology (Third Edition), 2010

2. Adams GE. Chemical radio sensitization of hypoxic cells. BrMed Bull 1973;29:48e53.

3. Fowler JF, Adams GE, Denekamp J. Radiosensitization of hypoxic cells in solid tumours. Cancer Treat Rev 1976;3:227e256

4.Hall EJ. Radiobiology for the radiologist. Philadelphia:Lippincott Williams & Wilkins, 2000.

5.4 Brown JM, Wilson WR. Exploiting tumour hypoxia in cancer treatment. Nat Rev Cancer 2004;4:437e447.

6.Horsman, M.R., Brown, D.M., Lemmon, M.J., Brown, J.M., Lee, W.W.: Preferential tumor radio sensitization by analogs of nicotinamide and benzamide. Int. J. Radiat. Oncol. Biol. Phys. 12: 1307-1310, 1986.

7.Horsman, M.R., Chaplin, D.J., Brown, J.M.: Radio sensitization by nicotinamide in vivo: A greater enhancement of tumor damage compared to that of normal tissues. Radiat.Res. 109: 479-489,1987.

8.Lawrence, T. S., Blackstock, A. W., & McGinn, C. (2003). The mechanism of action of radiosensitization of conventional chemotherapeutic agents. Seminars in Radiation Oncology, 13(1), 13–21. doi:10.1053/srao.2003.50002

9.1. Lawrence TS, Tepper JE, Blockstock AW: Fluoropyrimidine-Radiation Interactions in Cells and Tumors. Semin Rad Oncol 4:260-266, 1997

10.. Byfield JE: Useful interactions between 5-fluorouracil and radiation in man: 5-fluorouracil as a radiosensitizer. In Hill BT, Bellamy AS, eds: Antitumor drug-radiation interactions. Boca Raton, FL, CRC Press, 1990, pp 87-105

11.Lawrence TS, Davis MA, Loney TL: Fluoropyrimidinemediated radio sensitization depends on cyclin E-dependent kinase activation. Can Res 56:3203-3206, 1996

12.Axelson MD, Davis MA, Ethier SP, et al: HPV16-E7 expression causes fluorodeoxyuridine-mediated radiosensitization in SW620 human colon cancer cells. Neoplasia 1:177-182, 1999

13.. Boyer SN, Wazer DE, Band V: E7 protein of human papillomavirus-16 induces degradation of retinoblastoma

protein through the ubiquitin-proteasome pathway. CanRes 56:4620-4624, 1996

14.Wazer DE, Liu XL, Chu Q, et al: Immortalization of distinct human mammary epithelial cell types by human

papillomavirus 16 E6 or E7. Proc Natl Acad Sci U S A 92:3687-3691, 1995

15. Sawada N, Ishikawa T, Sekiguchi F, et al: X-ray irradiation induces thymidine phosphorylase and enhances the efficacy of capecitabine (Xeloda) in human cancer xenografts. Clin Can Res 5:2948-2952, 1999

16. Shirota Y, Stuhlmacher J, Brabender J, et al: ERCC1 and thymidylate synthase mRNA levels predict survival for colorectal cancer patients receiving combination oxaliplatin and fluorouracil chemotherapy. J Clin Oncol 19:4298-4304, 2001

17.Salonga D, Danenberg KD, Johnson M, et al: Colorectal tumors responding to 5-fluorouracil have low gene expression levels of dihydropyrimidine dehydrogenase, thymidylate synthase, and thymidine phosphorylase. Clin Can Res 6:1322-1327, 2000

18.. Lawrence TS, Chang EY, Hahn TM, et al: Delayed radio sensitization of human colon carcinoma cells after a brief exposure to 2', 2'-difluoro-2'-deoxycytidine (Gemcitabine). Clin Can Res 3:777-782, 1997

19.Lawrence TS, Chang EY, Hahn TM, et al.: Radio sensitization of pancreatic cancer cells by 2',2'-difluoro-2'-deoxycytidine. Int J Radiat Oncol Biol Phys 34:867-872, 1996

20. Rosier JF, Beauduin M, Bruniaux M, et al: The effect of 2'-2' difluorodeoxycytidine (dFdC, gemcitabine) on radiation-induced cell lethality in two human head and neck squamous carcinoma cell lines differing in intrinsic radiosensitivity. Int J Rad Biol 75:245-251, 1999

21. McGinn CJ, Shewach DS, Lawrence TS: Radio sensitizing Nucleosides. JNCI 88:1193-1203, 1996

22.Latz D, Fleckenstein K, Eble M, et al: Radiosensitizing potential of gemcitabine (2',2'-difluoro-2'-deoxycytidine) within the cell cycle in vitro. Int J Radiat Oncol Biol Phys 41:875-882, 1998

23.van Putten JWG, Groen HJM, Smid K, et al: End-joining deficiency and radiosensitization induced by gemcitabine. Can Res 61:1585-1591, 2001

24.Wachters FM, Kampinga HH, Van Putten JWG, et al: Gemcitabine selectively targets homologous recombination mediated DNA double strand break repair. Proc Am Assoc Can Res 43:149, 2002

25. Praetorius NP, Mandal TK. Engineered nanoparticles in cancer therapy. Recent Pat Drug Deliv Formul. 2007;1:37–51. [PubMed] [Google Scholar]

26. porcel E, Liehn S, Remita H, Usami N, Kobayashi K, Furusawa Y. et al. Platinum nanoparticles: a promising material for future cancer therapy? Nanotechnology. 2010;21:85103. [PubMed] [Google Scholar]

27. Ni J, Wu Q, Li Y, Guo Z, Tang G, Sun D. et al. Cytotoxic and radio sensitizing effects of nano-C60 on tumor cells in vitro. J Nanopart Res. 2008;10:643–651. [Google Scholar]

28. Jain S, Coulter JA, Hounsell AR, Butterworth KT, McMahon SJ, Hyland WB. et al. Cell-specific radiosensitization by gold nanoparticles at megavoltage radiation energies. Int J Radiat Oncol Biol Phys., 2011;79:531–9. [PMC free article] [PubMed] [Google Scholar]

29. Le Sech C, Kobayashi K, Usami N, Furusawa Y, Porcel E, Lacombe S. Comment on 'Therapeutic application of metallic nanoparticles combined with particle-induced x-ray emission effect' Nanotechnology. 2012;23:078001. [PubMed] [Google Scholar]

30 . Rabin HR,Urtasun RC,Partington J,Koziol D,Sharon M,Walker K ,Cancer Treatment Reports, 01 Oct 1980, 64(10-11):1087-1095 PMID: 7459894

31. Oya N, Shibamoto Y, Sasai K, Shibata T, Murata R, Takagi T, Iwai H, Suzuki T, Abe M: Optical isomers of a new 2-nitroimidazole nucleoside analog (PR-350 series): radio sensitization efficiency and toxicity. Int J Radiat Oncol Biol Phys. 1995, 33 (1): 119-127. 10.1016/0360-3016(95)00040-6.

32 . Kuwabara M, Iida Y, Inanami O, Sawamura S, Yokoyama K, Tsujitani M: Radiation-chemical properties of the hypoxic cell radiosensitizer doranidazole (PR-350). J Radiat Res (Tokyo). 2002, 43 (1): 77-88. 10.1269/jrr.43.77.

33. Aoki M, Furusawa Y, Shibamoto Y, Kobayashi A, Tsujitani M: Effect of a hypoxic cell sensitizer doranidazole on the radiation-induced apoptosis of mouse L5178Y lymphoma cells. J Radiat Res (Tokyo). 2002, 43 (2): 161-166. 10.1269/jrr.43.161.

34. Hamasu T, Inanami O, Tsujitani M, Yokoyama K, Takahashi E, Kashiwakura I, Kuwabara M: Post-irradiation hypoxic incubation of X-irradiated MOLT-4 cells reduces apoptotic cell death by changing the intracellular redox state and modulating SAPK/JNK pathways. Apoptosis. 2005, 10 (3): 557-567. 10.1007/s10495-005-1888-x.

35 . Shibamoto Y, Kubota T, Kishii K, Tsujitani M: Radiosensitivity of human pancreatic cancer cells in vitro and in vivo, and the effect of a new hypoxic cell sensitizer, doranidazole. Radiother Oncol. 2000, 56 (2): 265-270. 10.1016/S0167-8140(00)00181-X.

36. Murata R, Tsujitani M, Horsman MR: Enhanced local tumour control after single or fractionated radiation treatment using the hypoxic cell radiosensitizer doranidazole. Radiother Oncol. 2008, 87 (3): 331-338. 10.1016/j.radonc.2008.03.002.

37 . Yahiro T, Masui S, Kubota N, Yamada K, Kobayashi A, Kishii K: Effects of hypoxic cell radiosensitizer ornidazole (PR-350) on the radio response of murine and human tumor cells in vitro and in vivo. J Radiat Res (Tokyo). 2005, 46 (3): 363-372. 10.1269/jrr.46.363.

38. Sunamura M, Karasawa K, Okamoto A, Ogata Y, Nemoto K, Hosotani R, Nishimura Y, Matsui K, Matsuno S: Phase III trial of radiosensitizer PR-350 combined with intraoperative radiotherapy for the treatment of locally advanced pancreatic cancer. Pancreas. 2004, 28 (3): 330-334. 10.1097/00006676-200404000-00023.

39. Deeken JF, Loscher W: The blood–brain barrier and cancer: transporters, treatment, and Trojan horses. Clin Cancer Res. 2007, 13 (6): 1663-1674. 10.1158/1078-0432.CCR-06-2854.

40. Schneider SW, Ludwig T, Tatenhorst L, Braune S, Oberleithner H, Senner V, Paulus W: Glioblastoma cells release factors that disrupt blood–brain barrier features. Acta Neuropathol. 2004, 107 (3): 272-276. 10.1007/s00401-003-0810-2.

41. Towner RA, Smith N, Doblas S, Garteiser P, Watanabe Y, He T, Saunders D, Herlea O, Silasi-Mansat R, Lupu F: In vivo detection of inducible nitric oxide synthase in rodent gliomas. Free Radic Biol Med. 2010, 48 (5): 691-703. 10.1016/j.freeradbiomed.2009.12.012.

42. Pu AT, Robertson JM, Lawrence TS. Current status of radiation sensitization by fluoropyrimidines. Oncology 1995;9:707-14.

43. Pinedo HM, Peters GF. Fluorouracil: Biochemistry and Pharmacology. J Clin Oncol 1988;6:1653-64.

44. Herrick D, Kufe DW. Lethality associated with incorporation of 5-fluorouracil into preribosomal RNA. Mol Pharmacol 1984;26:135-40.