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Original Article

Application of Radiosensitizers in Cancer Radiotherapy, Nanomaterials of Heavy Metals, Drugs and Chemicals with Nanostructure

Muhammad Abbas Idris Nour[1], Zeina Ismail Abd-AL-Hassan[2], Dhiaa Haider Ibrahim Hassan[3]

[1,2,3]Al-Hilla University College/Department of Applied Medical Physics, Iraq

Abstract: High radiation doses are applied in radiotherapy (RT), a cancer treatment, to destroy cancer cells and reduce tumours. The intractable problem of increasing radiation damage to tumour tissue while minimising adverse effects to healthy tissue remains even with the tremendous success of radiotherapy. Chemicals and pharmacological substances known as radiosensitizers can speed up DNA damage and indirectly generate free radicals, therefore increasing the killing effect on tumour cells. Generally speaking, normal tissues are less affected by radiosensitizers. Low-toxicity, very effective radiosensitizers have been developed in recent years by utilising a number of approaches. First, we compiled in this study the uses of radiosensitizers, including those in clinical trials for small compounds, macromolecules, and nanomaterials. Second, a summary is given of the development states of radiosensitizers and potential ways to raise their sensitivity. Third, the opportunities and problems of radiosensitizer clinical translation in cancer therapy are discussed. With considerably less impact on healthy tissues, radiosensitizers are supposed to increase the death of cancer cells. Certain medications target distinct physiological features of the cancer, especially the hypoxia linked to radioresistance. The main hypoxic cell radiosensitizer is oxygen; the attraction of oxic versus hypoxic cells is their considerable differential radiosensitivity. Clinical potential is being shown by the combination of normobaric carbogen breathing and nicotinamide to alleviate acute hypoxia. Hypoxia-associated radioresistance may be universally combated by "electrical-affinic" compounds that react with DNA free radicals; nimorazole, a nitroimidazole, is clinically efficacious at tolerable doses. Tirapazamine and other hypoxia-specific cytotoxins are useful radiotherapy adjuncts. Strong hypoxic cell radiosensitizer nitric oxide is being produced; changes in endogenous amounts may have prognostic value. In theory, many medications can be selectively supplied to hypoxic tumours by activating the release of pharmaceuticals from electron-affinic prodrugs by reductase enzymes or by free radicals generated by radiation. Clinicians are testing a redox-active agent based on a gadolinium chelate. Iodine or bromine modified pyrimidines are integrated into DNA and increase free radical damage; fluoropyrimidines function differently. Many medications that affect the type or repair of DNA damage are being studied in combination with radiation; the processes underlying chemoradiation regimens are frequently unclear. Alkylating drugs include temozolomide; topoisomerase inhibitors (e.g., camptothecin, topotecan) and the hypoxia-activated anthraquinone AQ4N are also being studied. One powerful poly(ADP ribose)polymerase inhibitor under study is AG14361. Along with related kinases (drugs example vandetanib [ZD6474], cetuximab and gefitinib), and cyclooxygenase-2 (celecoxib), proteins involved in cell signalling, such as the Ras family, are intriguing targets connected to radioresistance.

Keywords: Radiosensitizers, Cancer radiotherapy, Therapeutics, Nanomedicine

Corresponding Author: Muhammad Abbas Idris Nour†, Al-Hilla University College/Department of Applied Medical Physics, Iraq

Introduction:

Undoubtedly one of the biggest threats to human health is still cancer. In 2015, the World Health Organisation (WHO) estimated that 8.8 million people died from cancer globally; the International Agency for Research on Cancer (IARC) predicts that number will rise to 13 million by 2030. Recent years have seen the development of a number of approaches to enhance cancer treatment, including surgery, radiation, chemotherapy, immunotherapy, targeted therapy, hormone therapy, stem cell transplantation, and precision medicine [1]. Since Nobel Prize winner Marie Curie discovered radioactivity, radiation (RT) has been regarded as one crucial and successful method for killing or controlling tumours.2 Usually, RT is a method of treating cancer cells with high-energy photon radiation, such gamma (γ)-rays and X-rays. RT can kill tumour tissue and cancer cells by both direct and indirect means.

Under the direct effect, radiation causes single-strand breaks (SSB) and double-strand breaks (DSB) in DNA, which stop cell division and proliferation or even cause cell necrosis and apoptosis. Under indirect action, radiation causes the production of reactive oxygen species (ROS), which can damage and stress biomolecules and eventually change cellular signalling pathways [1-2]. According to clinical research, over half of patients—roughly 70%—need RT, and in certain situations, it is the only course of cancer treatment.2 The requirement of developing methods to increase radiosensitivity is therefore enormous.

A different approach to raise RT efficiency can be offered by innovative technologies. To increase the accuracy and precision of treatment delivery, image-guided radiation therapy (IGRT) for instance uses imaging during radiation therapy. Tumours in moving bodily parts like the lungs can be treated with IGRT. Imaging capabilities built into RT devices let your doctor view the tumour both before and during treatment. The radiation beams and/or the patient's posture may be changed to more accurately target the radiation dose to the tumour by comparing these images to the reference images obtained during simulation. Some IGRT treatments include fiducial markers, ultrasound, MRI, X-ray imaging of bone structure, CT scan, 3D body surface mapping, electromagnetic transponders, or skin-colored ink tattoos to help align and target the radiation equipment.

Though the number varies by nation, 60–70% of cancer patients in Europe and the US now undergo radiation (RT) as part of their treatment [3]. The most effective and often utilised anticancer treatment is without a doubt radiation. Irradiation can, however, harm healthy cells and tissues close to the treatment site even if it might eradicate cancer cells. As such, precision RT has emerged as a significant trend in the advancement of RT technology to lessen the harm to normal tissues. Radiosensitizers (RSs) are becoming an essential component of the ionising radiation treatment of precise RT in the development of this technique. Radiosensitizers are medications used to increase the control and cure rates of cancer by increasing the sensitivity of tumour cells to radiation and increasing the efficiency of radiation in killing tumour cells. Direct and indirect mechanisms are principally at work. Cancer cells are damaged by direct radiation because of the physicochemical reaction between ionising radiation and reactive oxygen species (ROS). The indirect mechanisms are: (I) reducing the repair of radiation-induced DNA damage, so increasing the degree of DNA damage; (II) upsetting the cell cycle and organelle function to increase cytotoxicity; and (III) reducing the expression of radiation-resistant [4, 5] genes or increasing the expression of radiation-sensitive genes.

Radiotherapy with intensity modulation (IMRT)

A sophisticated type of high-precision radiation therapy (IMRT) delivers exact radiation dosages to a malignant tumour or particular regions inside the tumour using computer-controlled linear accelerators. While the therapeutic impact is much enhanced by the aforementioned cutting-edge technologies [5, 6], there are still challenges such cancer stem cells and tumour heterogeneity that make it challenging to treat tumours with RT alone. One effective approach to improve RT is likely to be the development of radiosensitizers that can pharmacologically reduce normal tissue toxicity and raise the radiosen-sitivity of tumour tissue.6 Compounds known as radiosensitizers do more to inactivate tumours when coupled with radiation than would have been anticipated from the combined action of each modality. Five categories were identified by radiosensitizer pioneer G E Adams: (1) suppression of intracellular thiols or other endogenous radio-protective substances; (2) formation of cytotoxic substances by radiolysis of the radiosensitizer; (3) inhibitors of repair of biomolecules; (4) thymine analogues that can incorporate into DNA; and (5) oxygen mimics with electrophilic activity.9,10 This classification pointed radiosensitizers in the right path early on and was based on the mechanics of DNA damage and repair. Nevertheless, an increasing number of substances and medications with

radiation sensitization have been classified as radio-sensitizers due to ongoing technical advancement. Furthermore, certain detailed radiosensitization pathways have also been identified.September 10 Small molecules, macromolecules, and nanomaterials are the three structural groups into which radio-sensitizers can be divided, according to the most recent study [6-11]. The applications, primary functions, and influencing aspects of these three radiosensitizer types—especially those that are presently undergoing clinical trials—are initially compiled in the section that follows. Furthermore summarised are the radiosensitizer's development status and mode of action. Thirdly, the future use and advancement of the radio-sensitizer were discussed.

Oxygen Mimics

Higher electron affinity and improved diffusion characteristics to anoxic tissue are features of oxygen mimetics, which use the chemical characteristics of molecular oxygen as a template [12]. Since oxygen mimics can supposedly replace oxygen in "fixing" radiation-induced DNA damage, rendering it irreversible and so fatal. As such, oxygen mimetics are regarded as "true radiosensitizers". Among the most representative oxygen mimics are nitric oxide (NO) and molecules containing nitrogen. Nitrobenzene is the paradigm of electron-affinity radiosensitizers; nitroimidazole and its derivatives are then the main focus of study [13–15]. Nitroimidazoles are compounds that redox reactions are induced by radiation and enzymes. These chemicals are inert by nature; ionising radiation is required for them to "fix" or stabilise DNA radical damages in cells lacking oxygen [16].

Among the first to be developed nitroimidazoles is misonidazole, a 2-nitroimidazole. In most solid mouse tumours studied in preclinical trials, misonidazole demonstrated a greater radiosensitizing impact than metronidazole (Flagyl®) or 5-nitro imidazole. In clinical trials, however, the results were disappointing because misonidazole caused serious neurotoxicity.Numbers 36–39 An inferior radiosensitizer has been shown to be metronidazole, a 5-substituted nitro-imidazole with weaker electron-affinity [17, 18]. Ultimately, metronidazole and misoni- dazole are not the best options for irradiation due to their dose-limiting toxicity at clinically acceptable levels.

Improved nitroimidazole pharmacokinetic characteristics have been sought for. Etanidazole and nimorazole are examples of second-generation nitro-imidazole radiosensitizers that work by increasing the reagents' hydrophilicity and therefore lowering neurotoxicity. Because hydroxyl modifies its side chain, etanidazole, for instance, has more hydrophilicity than misonidazole. While etanidazole has a reduced preclinical toxicity and greater efficacy, randomised trials have not clearly shown any benefit for individuals with head and neck cancer [19]. Since nimozole, a 5-nitroimidazole, has shown promise in multiple clinical trials, it is advised for the treatment of head and neck tumours in Denmark. It has also been investigated further in a multinational EORTC trial [20].

Remarkably, the DAHANCA 28 trial showed that patients may receive hyperfractionated, accelerated radiation (HART-CN) along with cisplatin and nimorazole and that the results were good tumour control.51 Furthermore used for hypoxia radiosensitization are other nitro chemicals. Now being assessed in the NCT02871843 clinic study, dinitroazetidine, RRx-001, has been shown to be a low-toxicity, efficient radiosensitizer.

Through several direct and indirect pathways, nitrogen oxides—NO in particular—act as radio-sensitizers. Through pathways of nitrosative stress, NO can "fix" or stabilise radiation-induced DNA damage, much as oxygen causes oxidative stress [21, 22]. Generation of reactive species is a component of the oxidative and nitrosative stress pathways. Through processes including DNA cross-linking, protein nitrosylation, glutathione depletion, and inhibition of mitochondrial respiration, nitrous acid, peroxynitrite (ONOO–), and nitric acid, for instance, cause harmful effects.

NO can freely diffuse across cell membranes as an uncharged free radical and bind to soluble guanylate cyclase (sGC) to stimulate the synthesis of cyclic GMP, hence controlling the physiology of the arteries. Researchers have shown that sanazoles and 5-nitroimidazoles can produce NO.60,63 Donating NO to patients with non-small-cell lung cancer (NSCLC) was shown in a phase I research to improve tumour perfusion and, consequently, tumour growth [23]. Low-dose NO, however, was shown in a phase II trial of prostate cancer patients to reduce hypoxia via increasing blood flow in tumour tissue, without having any direct lethal impact. Bevacizumab, sorafenib, and etaracizumab are examples of anticancer medications whose actions were partially attributed to their inhibition of the VEGF pathway by the US Food and Drug Administration (FDA) [24, 25]. Neovascularization and endothelial cell proliferation result from overexpression of VEGF in anoxic conditions. VEGF and NO have a positive and negative feedback regulation connection during angiogenesis that accurately preserves vascular homeostasis. Liebmann and colleagues also

demonstrated that pretreatment with NO increased the survival of irradiated mice.

Inhibitors of hypoxia

Because they are lethal to hypoxia cells preferentially, some bioreductive agents—such as aromatic N-oxides, transition metal complexes, quinones, aliphatic N-oxides, and nitro compounds—have radiosensitizing effects. Clinical trials of the hypoxia-selective radiosensitizer tirapazamine (TPZ) have produced encouraging results. Reductase in cells can convert TPZ under hypoxic conditions to a metabolite that generates free radical and causes base damage, SSB, and DSB on DNA.99 Pages Patients in a Phase I clinical study of radiotherapy and TPZ in small cell lung cancer survived longer [26, 27]. Patient response and failure-free survival were improved in a Phase II trial combining TPZ with chemoradiotherapy in locally advanced head and neck cancer. Further phase III studies using TPZ combined with chemoradiotherapy in locally advanced head and neck cancer, however, came to the conclusion that patient survival did not clearly increase.Chapter 102 Furthermore, the Drug Development Office of Cancer Research UK is now developing SN30000 (formerly known as CEN-209), an analogue of TPZ [28, 29] with better diffusion property that causes higher toxicity in hypoxic cancer cells than TPZ. A representative of aliphatic N-oxide, AQ4N, can be converted to AQ4 by nitric oxide synthase 2A or cytochrome P450 isoenzymes. In vivo studies revealed that, when AQ4N was combined with radiation, the anticancer effect was enhanced and the damage to normal tissue was much lower than with radiation alone. Results from Phase I clinical trials were likewise encouraging [30]. The selective activation of AQ4N in hypoxic areas of solid tumours was demonstrated in a Phase I clinical trial including patients with glioblastoma and head and neck tumours.

Radiosensitization is a property of TH-302 (evofosafamide), a related molecule that, in hypoxic conditions, can be converted to bromo-isophosphoramide mustard. Significant tumour development delay was achieved in preclinical models of NSCLC and rhabdomyosarcoma (skeletal muscle) by TH-302 in conjunction with radiation. Furthermore, a study using patient-derived xenograft models of pancreatic cancer showed that radiation combined with TH-302 was more effective than either therapy used alone. As TH-302 can target the hypoxia tumour cells preferentially and cause DNA damage in the surrounding tumour tissue of the hypoxic zone concurrently, it may have radiosensitizing effects in the therapy of solid tumours [31]. Only one of the 26 experiments (NCT02598687) on the US National Institutes of Health clinical trial database, however, offered combination treatment of TH-302 with radiotherapy; this trial was withdrawn because two phase III trials did not reach their primary endpoint.

DNA cross-linking is one way to activate the quinone-based anticancer drug mitomycin C. Other hypoxia-sensitive quinones selection is facilitated by the fact that mitomycin C only mildly harmed hypoxic cells in preclinical studies. Leading candidates among these are the bioreductive prodrugs porfiromycin (POR) and apaziquone (EO9). Preclinical research showed that POR has a greater hypoxic selectivity than mitomycin C. Even though preclinical studies showed POR had a tolerable toxicity, a Phase 3 trial that followed showed POR was less effective as mitomycin C. Preclinical research showed that EO9 can be a perfect radiosensitizer since it exhibited stronger anticancer activity than mitomycin C.

Products of nature

Some natural compounds are antioxidants with distinct effects on normal and malignant cells, whereby the radiotolerance of normal cells and the radiosensitivity of malignant cells may be increased. We carried out a survey and published a publication because the RS mechanism of a natural product with low toxicity and antioxidant effect is interesting; the radiosensitizing capacity of natural compounds was reported in this survey [31–33]. Among these natural substances are polysaccharides (Ganoderma lucidum polysaccharides, Wyer, brown algae sulfated dextran, ginseng polysaccharides, etc.), polyphenols (curcumin, quercetin, kaempferol, ellagic acid, etc.), alkaloids (berberine, (−)-Agelamide D, Hamala alkaloids, etc.), and other plant-derived extracts (ginsenoside and emodin). Selective enhancement of radiation toxicity in cancer cells is possible by molecular mechanism modulation. Radiation raises the amount of ROS in tumours and results in the killing of cancer cells directly [34]. Cancer cells are more prone to ROS induction therapy when their endogenous ROS levels are higher. These natural compounds can also work as antioxidants and lower ROS levels in healthy cells, therefore providing radiation protection. Releasing non-coding RNA, such as miRNA and LNC RNA, regulating the expression of radiation resistance proteins, such anti-apoptotic protein Bcl-2 and pre-apoptotic protein Bax, and selectively regulating the NF-κB pathway and induction of

autophagy death are the main indirect mechanisms [35]. Research to date has demonstrated that these natural compounds can raise the therapeutic index, lower adverse effects, and aid overcome drug resistance. There are still not many therapeutic uses for RT, though, given that people rarely ever fully absorb natural substances. A foundation for clinical trials of alternative combined medicines must be established by more investigation.

Leucines and Proteins

As radiosensitizers, proteins and peptides, such antibodies and short peptides, are useful because of their strong affinity with antigens and receptors over-expressed on the surface of tumour cells.Page 129 For example, the maytansine-based antibody-drug combination HER3-ADC targets HER3, induces cell arrest in the G2/M phase to prevent DNA damage repair and hence enhances radio-sensitivity in HER3-positive pancreatic cancer cells. The epidermal growth factor receptor targeting antibody SYM004 can reduce MAPK signalling, which reduces DNA double strand breaks repair and causes death, hence increasing radiosensitivity in tumour cells. By bindng to the epidermal growth factor receptor (EGFR), cetuximab and nimotuzumab can enhance radiation-induced DNA damage and death, hence increasing the radiosensitivity of human epidermal-like A431 cells. Most malignancies have increased expression of the hepatocyte growth factor (HGF)/Met signalling pathway, which facilitates DNA double-strand break repair.

Monoclonal antibody against HGF AMG102 can raise radiosensitivity of glioblastoma multiforme and prevent DNA damage repair. Furthermore, serum proteins and peptides such paraoxonase-2135, HSP134, and C-reactive peptide help to build radioresistance and can be targets for radiation therapy. HSP-70 and HMGB1 can help ECI301, a mutant form of macrophage inhibitory protein-1a, therefore increasing the effects of radiation.134 Furthermore enhancing the effects of radiation are other proteins such as NKTR-214,137 and DNAzyme (DZ1)136.

Oligonucleotides and microRNAs

Noncoding, single-stranded RNA molecules with around 22 nucleotides, microRNAs (miRNAs) are encoded by endogenous genes. Research has indicated that the effectiveness of radiation can be increased by using certain particular miRNAs.Radiotherapy sensitisation targets include 138,139 and some miRNAs.140 For instance, one can directly employ miR-621 tar-gets SETDB1 in hepatocellular carcinoma as a tumour radiosensitizer. Targeting the ubiquitin-conjugating enzyme Ubc13 and zinc finger E-box binding homeobox 1 (ZEB1), miR-205 increases the radiosensitivity of breast cancer cells. Targeting ATF2, miR-144-5p increases NSCLC radiosensitivity.No. 143 MiR-146a-5p activates the DNA repair pathway, which improves radiosensitivity in hepatocellular cancer. Radiation sensitivity is increased in NK/T cell lymphoma by miR-150 modulating the AKT pathway. MiR-99a increases NSCLC radiosensitivity by targeting the mTOR pathway. By suppressing several gene networks of DNA repair and ROS defence, miR-139-5p modifies radiation resistance in breast cancer.47 Cancer cells are induced to die by miR-320a transcriptional activation in the presence of ionising radiation.

NSCLC radiation sensitivity is increased, nevertheless, by miR-21-5p suppression. Targeting CDC14A directly, miR-630 inhibition increases radiation resistance in human glioblastoma. Moreover, a clinical investigation with 55 atypical meningioma patients revealed seven upregulated miRNAs (miR-4286, miR-4695-5p, miR-6732- 5p, miR-6855-5p, miR-7977, miR-6765-3p, miR-6787-5p) and seven downregulated miRNAs (miR-1275, miR-30c-1-3p, miR-4449, miR-4539, miR-4684-3p, miR-6129).

Oligonucleotides are crucial in the control of gene expression, much like siRNAs. Antisense oligonucleotides have a lot of promise to become radiosensitizers because they are simple to design and synthesis. Over 85% of tumours express telomerase, whereas normal tissues only express it to a limited extent. Radiolabeled oligonucleotides that targeted the RNA subunit of telomerase were shown to be able to suppress telomerase expression and cause DNA damage in telomerase-positive tumour cells. Furthermore, the reported promotion of radiation effect in liver cancer was achieved by phosphorothioate-modified anti-sense oligonucleotides (PS-ASODN) against human telomerase reverse transcriptase. Moreover, Park et al. found that tumor-specific radiosensitivity was increased by decoy oligonucleotide-based suppression of cyclic AMP response element-directed transcription. Yu and colleagues showed that radiosensitivity of nasopharyngeal cancer cells could be increased by antisense oligonucleotides directed against human telomerase RNA (hTR ASODN).

Materials and Nanomaterials of Heavy Metals

μ=ρZ4/(AE3), where ρ is the density and A is the atomic mass of the element, is the relationship between the X-ray absorption phenomena (E) and atomic number (Z).162 As so, the X-ray absorption coefficient (μ) changes significantly with the change of atomic number (Z). Effectively absorbing X-ray energy and interacting with radiation in tumour cells, noble metal nanomaterials like gold (Au, Z=79), silver (Ag, Z=47), and platinum (Pt, Z=78) release photoelectrons, auger electrons, compton electrons and other secondary electrons. Along with directly interacting with DNA, these secondary electrons also react with water to boost the synthesis of reactive oxygen species (ROS) and further raise the radiation sensitivity of tumour cells [36, 37]. It is a physical sensitization mechanism, this procedure.

Moreover, functionalized noble metal nanoparticles increase radiation sensitivity by promoting the production of reactive oxygen species (ROS), putting the cell cycle into a radiosensitive state, and blocking the p53 signalling pathway to cause cell autophagy and lysozyme body function disorder. It is a biological sensitization mechanism, this one. Sufficient radiosensitizing effects have been demonstrated in a variety of tumours by gold nanoparticles with good chemical stability, minimal toxicity, easy synthesis, variable size and shape, and simple surface functionalization. Furthermore often employed in biomedicine are silver and platinum nanoparticles [38, 39].

Thymoquinone-capping silver nanoparticles were described by Fathy recently as a promising tailored nanoformulation for improving cancer radiosensitivity.175 Platinum nanoparticles were shown by Li et al. to increase cell cycle arrest, ROS stress, and DNA damage, hence improving radiosensitivity. Furthermore demonstrated were the ability of platinum nanoparticles to change endogenic H2O2 in cancer cells to O2.

Like noble metal nanomaterials, gadolinium (Gd, Z=64), hafnium (Hf, Z=72), tantalum (Ta, Z=73), tungsten (W, Z=74), and bismuth (Bi, Z=83) are likewise large atomic coefficient metal elements with excellent X-ray attenuation properties. This is the reason that many research have concentrated on these heavy metal nanoparticles to look at its radiotherapy sensitization.

On direct touch, they typically injure healthy tissues, though. As such, the stable forms of them—oxides, sulphides, and selenides—are investigated as radiosensitizer. Most people refer to gadolinium-based nanoparticles as contrast agents for magnetic resonance imaging (MRI). Noteworthy is the discovery by researchers of the AGuIX family of gadolinium-based nanoparticles for radiosensitization and combined MRI [40]. The results indicated that, at a specific concentration, AGuIX might interact with X-rays and γ-rays. AGuIX can stay in the tumour for a long time after internalisation via the increased permeability and retention (EPR) effect, until the kidneys remove it. Preclinical animal studies demonstrated that AGuIX had clear radiosensitizing effects in multiple tumour models without any discernible side effects. Three clinical trials are being conducted: a single-arm phase II trial (NCT04094077) to assess the efficacy of AGuIX during fractionated stereotactic radiotherapy of brain metastasis; a Phase II clinical trial (NCT03818386) using AGuIX gadolinium-chelated polysiloxane based nanoparticles and whole brain radiotherapy in patients with multiple brain metastases; and a Phase I clinical trial (NCT03308604) to assess the optimal dose of AGuIX combined with chemoradiation in patients with locally advanced cervical cancer. Hafnium is chemical inert, belonging to the same family as zirconium and titanium. Usually, radioactive protective coatings, biosensors, and X-ray contrast agents employed hafnium dioxide (HfO2), the oxidation state of hafnium.

Drugs and Chemicals with Nanostructure

Researchers have recently shown great interest in nano-based delivery systems, which are effective methods for drug focused transportation and can deliver radiosensitizers including chemicals, oxygen carriers, siRNAs, and catalases to the tumour locations. Above all, radioactive particles such as 131I, 125I, and Ac (releasing a-particles) can be precisely delivered to tumour locations via nanobased delivery systems.223 Delivery of radiosensitizer has enormous potential with the advancement of nanotechnology. Clinical translation of nanobased delivery systems is still difficult to accomplish, nevertheless, as indications, radiation sources, and the physicochemical characteristics of the nanoformulations obstruct it [41, 42]. Long circulation lifetime of nanodelivery methods may also raise the chance of long-term harm. Stability of nanodelivery devices in bodily fluid is another important aspect.

Since the aggregation of nanoparticles in body fluid can affect the cellular reaction and pharmacokinetics as well as trigger major adverse consequences including blood vessel blockage. Designing the nanodelivery systems should therefore take these aspects into consideration. Furthermore significant is size; high Z and small nanoparticles

frequently have a greater radiosensitizing effect than larger ones. Particularly the positively charged tiny nanoparticles can easily be removed via renal clearance by binding to negatively charged DNA. Moreover, targeting and stability of nanostructures can be enhanced by functional modification with biocompatible materials.

Conclusions

From the first "free radical damage and fixation" techniques to gene control, from chemicals to biological macromolecules and nanomaterials, radiosensitizers have been produced for decades. The mechanics of sensitization are identical even if each radiosensitizer has unique benefits and drawbacks. The primary mechanisms are as follows: (I) reducing radiation-induced repair of DNA damage, hence increasing the degree of DNA damage; (II) upsetting the cell cycle and organelle function to enhance cytotoxicity; and (III) reducing the expression of radiation resistance genes or increasing the expression of radiation sensitive genes. Though certain nanora- diosensitizers have been applied for clinical research and small molecules, macromolecules, and nanoma- terial radiosensitizers are being produced, the results still fall short of clinical translation requirements. Finding new radiation targets and sensitization processes is therefore critically needed, followed by the development of more potent radiosensitizing medications. Firstly, researchers can concentrate on screening multitarget radiosensitizers or medication combinations because they frequently have more visible efficacy than single target. Promising new methods include nanotechnology based on radiosensitizers. Explored should be nanomaterials with minimal cytotoxicity, excellent biocompatibility, and simplicity of functionalization. Furthermore, other technologies that can quicken the creation of novel radiosensitizers include molecular structure analysis, molecular cloning technology, and bioinformatics analysis. Among them, sensitizers with active selectivity target particular or overexpressed receptors in the environment of cancer cells or cancer tissues; sensitizers with passive selectivity use the particular pH environment, hypoxic environment, and overgrown vascular structures of cancer tissue to accumulate in cancer tissue. Whereas passive selectivity mostly depends on variables like pH sensitivity and the molecular size of the drug itself, active selectivity mostly depends on the presence of certain receptors in cancer cells or the tumour microenvironment. Though there are currently few clinical trials, such selective RSs have promising futures in the field of precision cancer therapy. Researchers should continue to investigate their particular practical significance.

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