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Mechanism of Action and Use of Radiomimetic Compounds – Part 2

Radiomimetic Substances of Bacterial Origin

Abstract

Radiomimetic compounds, similarly to ionising radiation can directly or indirectly cause DNA damage. Two major groups of these compounds, alkylating agents and antimetabolites, have already been discussed in the first part of this article. The topic of this article is an overview of radiomimetic substances of biological origin; they are grouped and discussed upon their chemical structure. Some bacteria, belonging to the class of Actinobacteria can produce compounds with radiomimetic property as part of their defence mechanisms, such as bleomycins, enediynes, streptonigrins, etc. Radiomimetic compounds of bacterial origin can be divided into three main groups: radiomimetic glycopeptides, enediynes and quinone antibiotics. Each of them induces double-strand DNA breaks. Some of them work through their reactive radicals and the molecules are also transformed when they break DNA. Others, such as bleomycin and similar glycopeptides, have an enzyme-like catalytic effect as the molecule regenerates itself after interacting with DNA thus the same molecule can create new DNA breaks again. The damage caused by radiation and by bleomycin is very similar: double DNA strand breaks occur in close proximity to each other, below the lethal dose of the cell, so as the cell does not die, the DNA repair process is activated, which can lead to the formation of dicentric chromosomes and other detectable DNA alterations. This review briefly summarises the mechanism of action of bacterial radiomimetic compounds and their benefit.

Keywords: radiomimetic substances, bleomycin, alkylating agents, dicentric chromosome, enediyne

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Introduction

Changes that resemble the effects of ionising radiation have been observed during the usage of some chemical substances. The term radiomimetic was coined by Dustin in 1947; in 1952 Boyland made a list to summarise the features of radiomimetic compounds.[2] The first comprehensive review on this topic was published by Elson in 1963. That time only synthetic compounds were known to belong to this group. The radiomimetic substances of bacterial origin were discovered only a few years later.

In this second part of the article, they are grouped and discussed upon their chemical structure, as glycopeptides, enediynes and quinone antibiotics.

The first paper about bleomycin in 1966 found that some bacteria produce a compound with radiomimetic activity.[3] It was known earlier that many microorganisms producing antibiotics (e.g. penicillin, streptomycin) inhibit the growth and reproduction of other species via inhibiting polysaccharide synthesis or protein synthesis, but bleomycin was the first antibiotic with radiomimetic activity. Since then, many compounds with similar ability have been found and isolated.

The producing bacteria all belong to the class of Actinobacteria. They are gram positive, aerobic organisms, the colonies often grow extensive mycelia, like fungi, and the name of this phylum, Actinomycetales (the actinomycetes), reflects that they were earlier believed to be fungi. There are two exceptions: two enediyne compounds, shishijimycin and namenamycin, which are produced not by bacteria, but tunicates.

The earliest discovered enediyne, calicheamicin was isolated originally in the mid-1980s from the chalky soil, or "caliche pits", located in Kerrville, Texas.[4] The sample was collected by a scientist working for Lederle Labs. Later, in a monograph, researchers of Stanford University and Pfizer Pharmaceuticals argue that Alexander the Great was poisoned by drinking the water of the river Mavroneri (identified with the mythological River Styx) which is postulated to have been contaminated by this compound.[5]

Esperamycins were isolated in 1985, a family of extremely potent compounds showing a broad spectrum of antimicrobial and antitumor activity in murine systems has been identified in cultures of Actinomadura verrucosospora. The producing organism was collected at Pto Esperanza, Misiones, Argentina, consequently they named these compounds esperamicins.[6]

Mitomycin is an antitumor antibiotic discovered in the 1950s by Japanese microbiologists in fermentation cultures of the microorganism Streptomyces caespitosus.[7] Several close structural variants of mitomycins have since been isolated.

Many radiomimetic compounds act as alkylating agents, their alkyl groups are transferred to DNA during breakage. Only few chemicals, for example Streptonigrin, Bleomycin, m-AMSA can induce double-strand break (DSB). Chemically induced DSBs form acentric fragments, rather than dicentric chromosome (DIC). Due to its catalyst-like effect, bleomycin can induce DIC, which is considered widely an ionising radiation specific marker.

[2] Boyland 1952: 87.
[3] Umezawa et al. 1966: 200.
[4] Lee et al. 1989: 1070.
[5] Stoneman 2008.
[6] Konishi et al. 1985: 1605.
[7] Szybalski–Iyer 1964: 946–957.

In 1963 in his summary, Elson could not mention the formation of DIC as a radiomimetic effect (he only mentioned chromosome damage) because although bleomycin – which causes this specific effect of ionising radiation – has been isolated, it has not yet been published.

Characteristics of radiomimetic substances of bacterial origin

Radiomimetic compounds of bacterial origin can be divided into three main groups. Radiomimetic glycopeptides (such as tallysomycin and bleomycin), the second group is called enediynes (e.g. neocarzinostatin and C-1027) and the third is quinone antibiotics (anthracyclines, mitosanes [incl. mitomycins], streptonigrins and saframycins). It is important to note that not all compounds that belong to these three groups are radiomimetic substances.

The producing microorganisms are protected against the cytotoxic effects of the self-secreted compound, for example in their natural form, the radiomimetic molecules are often embedded in molecular chaperon proteins.

Radiomimetic glycopeptides: Bleomycin derivatives

While the structure of bleomycin derivatives exhibits similarities to other glycopeptides such as vancomycin, the pharmacodynamic pathways and mechanism of action of radiomimetic glycopeptides can be quite different and should not be confused with those glycopeptides which inhibit the synthesis of bacterial cell wall.[8]

Bleomycin (Figure 1), the first representative of radiomimetic glycopeptides (Table 1) was discovered in 1962 by a Japanese scientist Hamao Umezawa, who found an anticancer effect on the filtrate of the Streptomyces verticillus culture. He published this result in 1966.[9]

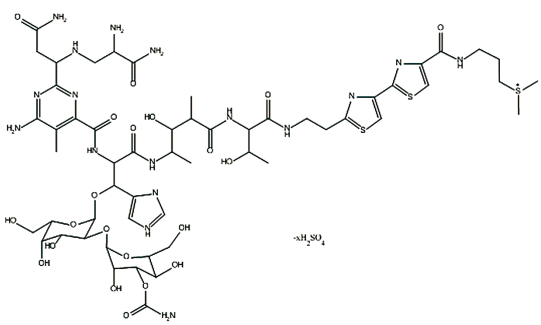

Figure 1: Bleomycin

Note: Bleomycin is a radiomimetic glycopeptide produced by Streptomyces verticulus. This molecule usually makes a complex with iron or copper ions.

Source: Soo et al. 2017: 1168.

[8] Andros et al. 2015: 1372.
[9] Umezawa et al. 1966: 200.

Table 1: Microorganisms producing glycopeptide antibiotics with radiomimetic effect

Producing organism	Antibiotics
Streptomyces verticillus	Bleomycin
	Phleomycins (zeocin)
Streptoalloteichus hindustanus	Tallysomycin
Streptomyces flavoviridis	Zorbamycin

Source: Coughlin et al. 2014: 6901.

Bleomycin and other natural glycopeptide antibiotics are non-ribosomal hybrid peptide-polyketide products. The peptide/polyketide/peptide chain of the aglycone is produced by the bleomycin megasynthase, which has both a non-ribosomal peptide synthase (NRPS) and a polyketide synthase (PKS) subunit. These non-ribosomal peptides and polyketides are made up of amino acids and short carboxylic acids by the above-mentioned bacterial enzymes.[10]

The cytogenetic effect of bleomycin has been known since the 1970s. Bleomycin is a large hydrophilic molecule and mostly unable to diffuse on biological membranes.[11] It enters the target cell after binding its receptor then it is transferred to intracellular endocytotic vesicles by receptor mediated endocytosis.[12]

Radiomimetic glycopeptides of bacterial origin require both metal ion [Fe (II), or Cu (I)] and molecular oxygen for their activity. It should be noted here that Fe^{2+} ions themselves have DNA damaging effects.[13] The glycopeptide molecule forms a complex with metal ions, which after that binds oxygen, as this connection is not stable it leads to the formation of free radicals and oxidised metal ions.[14] These reactive radicals can cause single strand breaks in DNA. Approximately every 10^{th} single strand break also has a second break on the adjacent DNA chain resulting in DSB.[15]

Based on the results of several studies, the cytogenetic effect of bleomycin is the most comparable to that of high linear energy transfer (LET) radiation, because in the case of high LET radiation, the distribution of cells with DICs is similar and the dose-effect relationship is also linear. It can be assumed that the high statistical variance observed after bleomycin treatment is due to different lymphocyte subpopulations and their different bleomycin sensitivity.[16]

At least two DSBs (i.e. 4 breaks) close to each other are one of the conditions for the creation of DIC. Most radiomimetic substances cannot produce close-to-each-other breaks at low – sublethal – concentrations, because the molecules are randomly distributed around the DNA and they themselves undergo an irreversible chemical transformation during the DNA break. In contrast, each Fe-bleomycin complex go through several cycles

[10] Arora et al. 2017: 99.
[11] Chen–Stubbe 2005: 102.
[12] Pron et al. 1993: 333.
[13] Ayene et al. 2007: 195.
[14] Dorr 1992: 3.
[15] Andros et al. 2015: 1372.
[16] Benkhaled et al. 2008: 134.

of oxidation and reduction and that bleomycin usually is not inactivated in the base-release reaction,[17] so one molecule can form many breaks and so DICs.[18] Ionising radiation causes DNA breaks by forming ions along a narrow straight line in nanosecond time as it passes through the DNA coil and in principle, any dose of ionising radiation, even a single track, can induce DIC. So, bleomycin acts the most similarly to ionising radiation amongst radiomimetic substances, as bleomycin can produce DIC effectively.[19]

Bleomycin does not interfere directly with DNA replication, thus acting independently of the cell cycle. Depending on which phase of the cell cycle interacts, it may also cause chromosomal and chromatid-type aberrations, but only slightly induce exchange between sister chromatids.[20]

Bleomycin can be metabolically inactivated in normal and tumour tissues by an enzyme called BLM hydrolase,[21] or it can be inactivated by an N-acetyltransferase which inactivates the drug in the presence of acetyl coenzyme A.[22]

Enediynes

Since the discovery of calicheamicin (Figure 2) and esperamycin, several enediynes produced by various bacteria have been discovered.[23] Synthetically produced enediynes have also been created to improve the functionality of naturally occurring molecules (in contrast to bleomycin derivatives, enediynes are not oligopeptides but polysaccharides). The central ring of these molecules contains an alkene conjugated with two alkynes.[24] This ring has a total of nine or ten members.[25] Other functional groups are usually attached to these central rings, providing each enediyne with additional chemical properties.

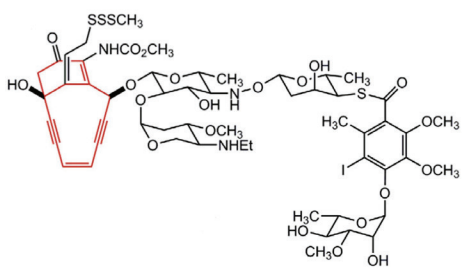

Figure 2: Calicheamycin

Note: Calicheamycin is an enediyne with a ten membered ring produced by Micromonospora echinospora.

Source: compiled by the author.

[17] Povirk 1979: 3989.
[18] Benkhaled et al. 2008: 139.
[19] Hoffmann–Schmitz-Feuerhake 1999: 118.
[20] Benkhaled et al. 2008: 138.
[21] Galm et al. 2005: 741.
[22] Sugiyama et al. 1994: 81.
[23] Lee et al. 1987: 3464.
[24] Nicolaou et al. 1993: 5881.
[25] Galm et al. 2005: 744.

There are 11 naturally occurring enediynes, and three others have been isolated in cycloaromatised form;[26] the other molecules are produced synthetically.

Enediynes can be divided into two groups based on the numbers of the central ring's members (9 or 10) (Table 2).

Table 2: Enediynes with nine- and ten-membered cores and their origin

Enediynes	Origin
Nine-membered ring	
Neocarzinostatin	*Streptomyces carzinostaticus*
C-1027 (lidamycin)	*Streptomyces globisporus*
Kedarcidin	*Actinomycete sp.*
Maduropeptin	*Actinomadura madurae*
N1999A2	*Streptomyces sp.*
Ten-membered ring	
Calicheamicin	*Micromonospora echinospora*
Dynemicin	*Micromonospora chersina*
Esperamicin	*Actinomadura verrucosospora*
Shishijimicin	*Didemnum proliferum*
Uncialamycin	*Streptomycete sp*
Golfomycin A	synthetic
Taxamycin	synthetic

Source: compiled by the author.

Another name for enediynes with nine-membered ring is chromoprotein because they are associated with an apoprotein. Apoprotein is required for transport and stabilisation of the labile chromophore enediyne group.[27] The histone specific protease activity has been examined for Neocarzinostatin (NCS)[28] and results confirmed that protease activity can be separated from NCS-A (apo-protein), suggesting this activity is due to minor contaminating proteases.[29] NCS and C-1027 consist of hydrophobic proteins that require the presence of enediyne prosthetic groups for activity. NCS is a natural product of Streptomyces carzinostaticus. This chromophore forms a chromoprotein with a 113-amino acid polypeptide.[30] Two possibilities emerged to consider: the apo-protein has cofactor for protease activity that is lost (perhaps the enediyne itself) or could bind a specific protease by noncovalent interactions.[31]

In addition, organisms that produce enediynes have been shown to protect themselves with a self-resistance mechanism that uses a self-sacrificing protein. Some microbes that produce calicheamicin use CalC (a peptide encoded by the gene

[26] Shen et al. 2015: 10.
[27] Gao–Thorson 2008: 105.
[28] Heyd et al. 2000: 1812.
[29] Gao–Thorson 2008: 105.
[30] Heyd et al. 2000: 1812.
[31] Galm et al. 2005: 747.

CalC from the calicheamicin biosynthetic gene cluster) as defence mechanism, so the diradical absorbs hydrogens from a glycine of the protein, not from the DNA.[32]

One of the most significant properties of enediynes is their limited anti-tumour and antibiotic activity. They effectively induce apoptosis in cells but cannot distinguish between healthy and tumour cells.[33]

Enediynes bind to DNA by interaction with the minor groove and activate to DNA-cleaving biradical species, either by reaction with thiols or by reduction.[34]

In this step, enediynes generate free radicals. The chemical basis for enediyne activation is the Bergmann reaction, through which enediyne systems undergo cycloaromatisation to benzene derivatives, with the intermediacy of the highly reactive 1.4-benzenoid biradical species. In the related Myers reaction, (e.g. in case of neocarzinostatin) one of the triple bonds can be replaced by an allene unit, leading to biradical as well. The result a 1.4-benzenoid biradical is highly reactive, abstracting all hydrogen from all possible hydrogen donors.

During interaction with DNA, the 1.4-benzenoid diradical displaces hydrogen from the phosphate-deoxyribose backbone, predominantly from the C-1', C-4' and C-5' positions. Hydrogen removal causes radicalisation on the affected carbon. Carbon radical reacts with molecular oxygen, which causes chain breakage in DNA by various mechanisms.[35]

The 1.4-benzenoid diradical can position itself to abstract hydrogens from both strands of DNA close to each other.[36] This leads to a DSB that may result in apoptosis if not repaired.

This process is even more efficient at producing DSBs than the free radicals produced by radiomimetic glycopeptides: DSBs occur in approximately 1:8 of interactions with NCS, 1:1.8 with C-1027 and 1:2 with Calicheamicin.[37]

Quinone antibiotics

Quinone is a highly bioreactive moiety, it is found in many variants in bacteriostatic compounds, known as quinone antibiotics.

Four main groups of quinones of bacterial origin that cause DNA damage are anthracyclines, mitosanes, streptonigrins and saframycins.[38] A few representatives of antracyclines, doxorubicin and daunorubicin were reported as radiomimetic compounds,[39] as well as mitomicins[40] and streptonigrin.[41] Almost all of quinone antibiotics

[32] Liang 2010: 501.
[33] Grdičak–Jerić 2007: 134.
[34] Avendaño–Menéndez 2008: 376.
[35] Povirk 1996: 78.
[36] Kraka–Cremer 2000: 8246.
[37] Andros et al. 2015: 1372.
[38] Lown 1983: 21.
[39] Lu–Yagi 1999: 263.
[40] Almodin et al. 2013: 110.
[41] Sánchez et al. 2010: 90.

generate reactive oxygen species or alkylate the DNA. A few of them need metal ions to function.

Anthracyclines are antibiotics and have broad-spectrum antitumor activity. They inhibit cell function at three main points: the nucleic acid metabolism, the integrity of cellular phospholipid membranes and the redox reactions. The latter includes cellular respiration and electron transport. The aglycone moiety of daunorubicin and doxorubicin has been shown to intercalate between base pairs of the DNA helix.[42]

Streptonigrin is an aminoquinone antibiotic produced by Streptomyces flocculus. The cytotoxic effect is based on the formation of free radicals and the inhibition of topoisomerase II activity.

Mitomycin (MTM) A and B were isolated from Streptomyces caespitosus in 1956,[43] and shortly after mitomycin C was found from the same strain.[44] Of all these different MTMs, mitomycin C led to early, widespread clinical application due to its uniquely outstanding activity and reduced toxicity against solid tumours compared to the natural counterparts of mitomycin A and mitomycin B.

Because mitomycin C is isolated from Streptomyces, it belongs to the radiomimetic substances of bacterial origin. In respects of mechanism of action, it is also an alkylating agent.[45] A unique feature of MTMs is that they are converted to the active ingredient by an enzyme reduction process, preferably in the absence of oxygen; MTM C can be reductively activated by several oxidoreductases, in a process required for the expression of its therapeutic effects. This enzymatic reduction results in preferential activation of MTM C under hypoxia and, in most instances, the production of greater toxicity to oxygen-deficient cells than to their oxygenated counterparts,[46] so that MTM C is mainly active under anaerobic conditions.[47] Unlike BLM and enediyne antibiotics, MTM does not directly cause DNA backbone breakage, but rather forms covalent bonds with DNA and acts as an alkylating agent, coupling DNA with high efficiency, specifically CpG sequence (CpG sites are regions of DNA where a cytosine nucleotide is followed by a guanine nucleotide in the linear sequence of bases along its 5' – 3' direction). The degree of cross-linking of the DNA interstrand increases with GC content.[48] MTM C is a potent antibiotic that belongs to the family of antitumor quinones and has high efficacy in the treatment of solid tumours. Unfortunately, acquired or intrinsic drug resistance in tumour cell populations limits the utility of the drug.[49] The side effects of MTM suggest a radiomimetic nature, as the main toxicities are thrombocytopenia and leukocytopenia. Rare but serious side effects are hemolytic uremic syndrome, pneumonia and heart failure.[50]

[42] Lown 1983: 21.
[43] Hata et al. 1956: 141.
[44] Hata–Sugawara 1956: 147.
[45] Sastry et al. 1995: 338.
[46] Sartorelli et al. 1994: 501.
[47] Verweij–Pinedo 1990: 6.
[48] Galm et al. 2005: 753.
[49] Galm et al. 2005: 752.
[50] Verweij 1990: 8.

Some of the saframycin antibiotics can alkylate DNA via forming electrophilic imine species. Only those saframycins can alkylate the DNA that bear a leaving group (i.e. cyanide or hydroxide).[51]

Application of radiomimetic compounds

Antibiotic activity

The effect of radiomimetic compounds on different types of cells may vary, but their selectivity is still poorly understood.[52]

Bleomycin and Tallysomycin show general activity against Gram-negative bacteria, while radiomimetic enediynes are generally more active against Gram-positive bacteria.[53]

Many quinone antibiotics show both radiomimetic and antibacterial properties. Streptonigrin has anti-bacterial activity against E. coli. Mitomycin A, B and C together with porfiromycin and many of their analogues exhibit useful antibacterial properties against Gram-positive and Gram-negative bacteria.[54]

Tumour and autoimmune therapy

It was mentioned in the first part of this article how chemotherapy began with the nitrogen mustard. Radiomimetic glycopeptides are widely used in the treatment of germ cell line cancers and lymphomas.[55] Bleomycin and its derivatives are also used in cancer therapy regimens, e.g. in the BEP regimen: bleomycin, etoposide and platinum agents are used for treatment testicular cancer and germ cell tumours.[56]

Bleomycin is used in the chemotherapy of several types of cancer, such as certain lymphomas and skin cancers.[57]

In the case of enediynes, excessive cytotoxicity limits the utility of them, and the development of less toxic analogues is the subject of research. In general, most of the enediynes are too toxic to be used for clinical purposes; although neocarcinostatin and calicheamicin are used in a limited extent.[58]

Many efforts have been made to increase the cancer therapeutic specificity of these drugs by altering their tissue distribution. Attempts were taken nowadays assembling enediyne-integrated fusion proteins, containing defensin which is a ligand of epidermal growth factor receptor.[59] Calicheamicin is extremely toxic to all cells and,

[51] Gates 1999: 497.
[52] Andros et al. 2015: 1377.
[53] Andros et al. 2015: 1377.
[54] Lown 1983: 25.
[55] Andros et al. 2015: 1372.
[56] Cafferty et al. 2020: 139.
[57] Groselj et al. 2018: 120.
[58] Avendaño 2008: 377.
[59] Liu et al. 2018: 1538.

in 2000, a CD33 antigen-targeted immunoconjugate N-acetyl dimethyl hydrazide calicheamicin was developed and marketed as targeted therapy against the non-solid tumour cancer acute myeloid leukemia (AML).[60] A calicheamicin-linked monoclonal antibody, inotuzumab ozogamicin (marketed as Besponsa) an anti-CD22-directed antibody-drug conjugate, was approved by the U.S. Food and Drug Administration in 2017, for use in the treatment of adults with relapsed or refractory B-cell precursor acute lymphoblastic leukemia.[61] Today, antibody-drug conjugates still have a relatively narrow therapeutic index, but the design of new types of molecules can improve this. During the development of antibody-drug conjugates in cancer therapy, pharmacokinetic/pharmacodynamic modelling provides significant assistance in achieving the desired pharmacokinetic properties and therapeutic index.[62]

Mitomycin is widely used in different chemotherapy regimens for gastric, breast and lung cancer and mesothelioma. It is not absorbed through the bladder mucosa, when given intravesically. It is used to treat superficial carcinoma of the bladder.[63]

Diagnostic tests, experimental models

Some radiomimetic agents are also used in vitro or in animal models for diagnostic or research purposes. For these methods, these compounds were not necessarily selected based on their radiomimetic features, but in many cases for their other chemical properties.

Without attempting to be comprehensive, a few samples of these research topics can be found in Table 3.

Table 3: Radiomimetic agents used as research tools

Compound	**Application**
Bleomycin	Ex vivo test for determining chromosome breaking susceptibility[64]
	Inducing lung fibrosis (in mouse)[65]
	Detection of the iron content of serum[66]
Methotrexate	Cell division synchronisation in cell culture[67]
Streptozotocin	Animal model for diabetes[68]
Diepoxybutane	Ex vivo test for determining chromosome breaking susceptibility (Fanconi anemia)[69]

Source: compiled by the author.

60 Ellestad 2011: 660.
61 ASH Clinical News 2018: 26.
62 Lin et al. 2018: 22.
63 Jacob 1996: 266.
64 Székely et al. 2003: 59.
65 Song et al. 2015.
66 Buffinton et al. 1986: 65.
67 Sen 1990: 595.
68 Graham et al. 2011: 356.
69 Auerbach 2015: 8.7.1.

Conclusion

Since Elson's summary in 1963, many compounds have been discovered that have a radiomimetic effect, albeit with different mechanisms. This significantly complicated the interpretation of the concept. In this summary, I have described the compounds that could not have been included in Elson's work, since they were discovered only later. These are molecules of bacterial origin that play a role in the defence mechanisms of microorganisms. These compounds are capable of exerting their radiomimetic effect by different mechanisms compared to those previously described, so the biological effects listed by Boyland cannot be fully applied to them either.

Today, according to many, "radiomimetic substances" are not considered to be a category that acts as listed by the original descriptors, rather, a group of compounds that damage nucleic acids and may be useful in the treatment of cancer. However, this definition excludes compounds that have no therapeutic use but have been shown to be radiomimetic in their activity.

The field of application of radiomimetic substances is constantly expanding. Radiomimetic compounds can do good service in many areas of life, especially in medicine. Most radiomimetic substances are used in the treatment of various types of cancer or as cytotoxic agents, antibiotics or immunosuppressive compounds. Their use may partially or completely replace radiation or optimise the dose in the case of radiation therapy. Radiomimetic substances cannot even partially play the role of X-ray in diagnostic imaging methods because they do not emit detectable radiation, so physical dosimeter is not able to detect any exposure from them, in contrast to isotopes or isotope labelled diagnostic and therapeutic compounds. However, they are useful in in vitro diagnostics (e.g. determination of blood iron level and chromosome fragility, diagnosis of Fanconi anemia). They have also proved useful in preclinical research on various future drugs to produce of animal models.

According to the original symptomatic-like interpretation, radiomimetic substances mimic the biological effects of ionising radiation. Some refinement is recommended, keeping only compounds that are effective in humans as radiomimetic substances. This group can also be assessed in the context of use and mechanism of action. Their use in cancer therapy is common, but not all of them are suitable for medical use yet, so this is not a necessary condition for the name. Their DNA-damaging effects are expressed at the molecular level directly by the formation of alkyl groups or reactive oxygen species (ROS), or indirectly by the inhibition of DNA-maintaining enzymes. The final image is formed with DNA repair enzymes from surviving cells; these are chromosome breaks, chromatid translocations, deletions and mutations. Some of these changes persist or are passed on to progeny cells through division.

Given that the formation of DIC is the only effect what can be considered specific to ionising radiation, it is worth considering that this phenomenon should also be added to the list of radiomimetic effects.

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