A New Approach to Cancer Remedy by Radioimmunotherapy with Alpha Particles: A Novel Study

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Abstract— Radioimmunotherapy (RIT) with alpha particles which have high linear energy transfer (LET) rate and short range and cause to death of cells only by a few strikes is very suitable for controlling of metastatic diseases, hematologic malignancies such as various types of leukemia and lymphoma and local remedies of cancer such as intraperitoneal remedy. Among the suitable radioisotopes for remedial actions, 213Bi is of most application due to its availability via 225Ac – 213Bi generator. The pharmacokinetic of RadioImmuno Conjugate (RIC) is complex and difficult to predict. This issue is directly depending on the tumor type, relative affinity and type of Monoclonal Antibody (MAb). Various methods have been introduced for increasing the concentration in tumor and decreasing it in sound cells such as pretargeting methods, using RICs as liposomal, using the radionuclides which have special absorption in tumor cells and applying of blocking factors of β-Adrenergic. To obtain a scale for dosage of applied drug, it is necessary to understand the condition of interaction between alpha particles within the cell by microdosimetry. But, it is usual to determine the macroscopic distribution of radioisotopes by imaging or sampling methods and then, to calculate the dosage of various organs by mathematical models or simulating methods. The clinical experience of this method has been initiated since 1996 and research groups reported the improvement of various types of cancer with minimum side effects. Currently, various researches is under consideration for optimizing the RIC compound and its dosage in order to mass production of such radiodrugs.

Index Terms— Alpha particles, Radioimmunotherapy, Radioimmunoconjugate, Dosimetry, Microdosimetry, Cancer remedy, Linear energy transfer

1 Introduction

The traditional methods for cancer remediation such as radiotherapy and chemotherapy are not assignable and they cannot be considered as a healing remedy due to their toxic effects on sound cells. There have been many efforts to increase the remedy index, i.e. the ratio of the effect of remedial action on tumor to sound cells, and in this regard, two strategies are usually adopted: local use of drug and linking of cytotoxic factor to a carrying molecule which is acted specifically or preferentially in cancerous cells. Hence, targeted radionuclide therapy, i.e. use of drugs including radioactive, which may be included various types of radiations such as alpha, beta and gamma with various energies and be targeted the cancerous cells based on their anatomic or biochemical characteristics, is applied for increasing of toxicity in cancerous cells. In most clinical applications, beta radiative radionuclides such as 90Y and 131I are used which left their energy in a few millimeters length. As a result, this type of radiation is suitable for remediation of relatively large tumors [1-8]. At the other hand, one of the most important issues in cancer management is controlling of metastatic disease. This goal is gained by replacing of radiant energy in cell dimensions; hence, alpha particles (nucleus of helium), which loosed their energy speedily and at a distance of about the diameters of a few cells, are seemed to be very suitable toxic agents [9-19].

After selecting of a suitable radionuclide for targeted radionuclide therapy, the carrier and targeting agent should be selected. Various types of chemical compounds can be used in this regard such as: (1) particulate agents such as colloids, microspheres, and liposome and (2) monoclonal antibodies (MAb). The first group of targeting agents work by direct injection of drug in a part of body that is isolated and tumor is presented in that part (local remediation). However, monoclonal antibodies are better options for targeted radionuclide therapy by alpha particles since: (1) They are able to recognize the receivers of cell surface, (2) They are chemically compound, well, with many of radionuclides that radiate alpha particles, (3) The biological distribution of radioimmunoconjugate, composition of MAb with considered radionuclide, has not any difference with distribution of MAb prior to labeling (before compounding with radionuclide) and (4) There are numerous antibodies – antigens for remedial applications in various types of cancers [20].

Therefore, RIT with alpha particles, i.e. treatment by radionuclides that radiate alpha particles which targeted cancerous cells with MAbs, is considered during two last decades as a new and promising method for cancer remediation.

In this paper, different aspects of RIT with alpha particles are considered. But, at first, the quantities, concepts, tools or methods that are mentioned in the text should be defined.

(a) Absorbed dose (D): the transferred energy by radiated particle (here, alpha particle) to unit mass of material during movement in the physical media. The biological effects of radiation are directly dependent on this factor.

(b) Dosimetry and Microdosimetry: the measuring of absorbed

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dose and its related quantities to estimate the effects of ray in centimeter (dose for organs) and micrometer (dose for cells).
(c) Linear energy transfer (LET) rate: the amount of energy transferred by a particle to a material per unit distance. It is usually explains in terms of kilo electron volt per micrometer (keV/μm). Similar to absorbed dose, it has a direct relationship with biological effects of radiation.
(d) Relative biological effectiveness (RBE): the ratio of the absorbed dose for a reference ray to the absorbed dose for considered ray to create a given biological effect in a same condition. This factor depends on the type and energy of radiated particle and also on conditions of study. Higher RBE is equivalent to more biological effects [20, 21].
(e) Reactor: a chamber for performing nuclear reactions wherein necessary conditions for performing the reaction is provided and the security and safety issues are adopted.
(f) Accelerator: a chamber wherein charged particles such as electrons, protons and or ions accelerated by electromagnetic fields. These particles can results nuclear reactions when they collide with nucleus.
(g) Decay chain: a set of successive nuclear reactions happened in the nature and lead to transforming of unstable radionuclides to stable nucleuses.
(h) Parent nucleus and daughter nucleus: the daughter nucleus is resulted from decay of parent nucleus.
(i) Generator: a means that the parent nucleus with long half-life is placed in it and the daughter nucleus is separated from it with chemical methods and in regular time intervals and finally is used for medicine purposes.
(j) Gamma camera: it is the most usual tool for providing images from distribution condition of radionuclides in the body which determines the location and concentration of radionuclide by receiving the gamma ray radiated from the injected radiodrug.
(k) Positron Emission Tomography (PET): an advanced method for imaging with very high resolution which works based on the revelation of photons induced by compounding of positron, which radiated from the injected radiodrug. The presented electron in the material shows the distribution of radiodrug.

2 RESULTS AND DISCUSSION

The suitable radioisotope for clinical applications should have the following characteristics: (1) It should be available, purely and with reasonable price; (2) It should have suitable decay characteristics; (3) Its physical half-life should be enough long so that RIC can penetrate and it should be compatible with pharmacokinetic replacement of RIC in the tumor location; (4) It should have a fast and stable connection to MAb; (5) It should have, as a relative advantage, a Gamma radiation with suitable energy for imaging which facilitates the study of biological and dosimetry distribution. Among the about 100 alpha emitter radionuclides, only a few ones are suitable for remedial applications. The accesses to the radionuclides are provided by two ways: (1) Via the natural decay chains, the considered radionuclide is the product of these decays. In some cases that the parent nucleus has a long half-life, it may design and use the specific generator of that reaction; (2) Via the nuclear reactions within the accelerators or reactors.

The pharmacokinetic of RICs are complex and difficult to predict since all parameters of biological system are interfered. This issue is directly related to tumor type, relative affinity and type of MAb. For example, large antibodies such as IgM or IgG need one to two days to focus and their lifetime are more than two weeks. However, in cases of micrometastasis presented in blood flow and or hematologic malignancies such as various types of leukemia and lymphoma, RICs received to the considered location in the body a few minutes after intravenous injection. The molecular weight also is important due to obtaining the desired ratio of absorption of considered cells to absorption of unconsidered cells in the glomerular filtration rate and to obtaining minimum toxicity of sound cells. The physical half-life of radionuclides should be 1.5 to 3 times longer than the necessary time to maximizing the absorption of RIC.

For increasing the concentration of radiodrugs in under remediation cells and decreasing it in other cells, various strategies are followed. Use of elements with special absorption in specific cells is desired. For instance, "Alpharadin TM", which is produced by "Algeta" Corporation, used 223Ra, an alkaline earth metal with special absorption in bone (same as Calcium), for remediation of skeletal metastasis [22-25].

Use of bispecific antibodies which allow "pretargeting" is of interesting results. In this method, drug is used in two steps. In the first step, the non-radioactive target antibody injects. This antibody connects to tumor receivers and locks them. The free antibodies clear from system. In the second injection, RIC injects. RIC has a connecting part which connects to the un-locked arm of bispecific antibody. It leads to minimizing the amount of RIC in blood flow.

In addition, pharmacologic interferences are used to increase the concentration of RIC in tumor and decrease it in sound cells. For example, applying of blocking agents of β-Adrenergic which reduce the heart output to the ineffective sound cells to blood flow within the enervated vessels is possible [22-26]. In another method, the researchers encapsulated the compound of RIC including 225Ac nucleus which has four successive alpha decays (225Ac➔ 221Fr➔ 217At➔ 213Bi/213Po) to reserve daughter nucleuses in the location of parent nucleuses and to increase absorbed dose within the liposome. This method may be suitable for local – regional remediation such as intraperitoneal remedy, liver artery and or spinal casing [26].

To pharmacokinetic study of alpha particles with short lifetime, imaging and/or sampling should be performed immediately after RIC injection. For imaging with Gamma camera, the considered photon energy of radionuclide should be in the working range of radiotherapy imaging tools. In this regard, 149Tb is the best option which its Gamma ray is comparable with 99mTc. Further, 149Tb radiates positron which can be useful in PET imaging. For radioisotopes with unsuitable Gamma ray for imaging, the radioisotope can be connected to MAb. For example, 111In accompanied by antibody 7,16,4 has been used to investigate the metastasis of breast cancer [27, 28].

Dosimetry is performed by different methods and in different levels but its final goal is common which is calculating the

received dose to tumor and sound cells, estimating its effects and obtaining to a suitable scale of dose or treatment planning.

This type of dosimetry is used for estimating the risk level of immunotherapy and establishing a balance between hurts of cancerous and sound cells. The tumor dose is restricted by maximum tolerable dose by normal cells. The organ which restricts dose is different in different methods and different utilized RIC. For instance, marrow restricts the dose in systemic remediation and for radionuclides with short lifetime kidneys can be subjected to danger. The dosimetry in scale of organs is founded by Medical Internal Radiation Dose (MIRD) committee. In the scheme of this committee, source organs (ideally, tumor or cancerous cells) and target organs (other organs) define and then, absorbed dose calculates in terms of a part of source energy which is absorbed by target and a little amount of radiodrug concentration in the source which obtains from sampling or imaging methods. In addition to recommended methods by MIRD committee, which some commercial software are supplied to the market based on these methods, researchers estimate the amount of dose for organs and its effects by considering various physical and biological parameters. For example, Atthey et al. by studying the reliving and reproduction of cells concluded that decrease in physical half-life of radiodrug increases the probability of tumor control [29-41]. Hamacher and Sgouros represented a formula for estimating the absorbed dose induced by 225Ac by considering the daughter nucleuses and their specific biological distribution, systematic flow of radiodrug, cellular models and so on [42-47].

A true understanding from sensitivity of sound and cancerous cells to radiation is a prerequisite for evaluating the effectiveness of remediation. The dosimetry in cellular level is performed by calculative methods and nucleus, usually, is considered as the main target of radiative damage in cell which leads to sterility of cell [48, 49]. In addition, it can be possible that used from autoradiography, i.e. histologic cuts which shows the distribution of radioactive material within the cut, for obtaining images with high resolution from radionuclide distribution in under-cell level and then, the obtained information input to the microdosimetric calculations [50].

The calculations are performed in DNA level and nanometer scale by simulation. For instance, DNA simulates by cylinders with 1 to 100 nanometer diameter and the remained energy from alpha particles within DNA and then, the probability of failure in DNA string obtain and finally, values of relative biological effectiveness (RBE) assign.

In spite of increasing accuracy in calculations, absorbed dose cannot be accurate since the quantitative distribution of radionuclide and its time of travelling in the body are measured approximately due to limitation of accuracy in physical measurements. Even if it possible to calculate dose, approximately, the biologic results, risks and remedial effects can only be estimated because of biological complications.

Anyway, while the mentioned restrictions are remained, dosimetry is used for estimating possible risks and establishing cautionary limits for radionuclides, designing of remediation and studying of unusual synthetic remedial methods such as remediation by several RICs or synthesizing the remediation action by x ray and remediation by radionuclides (e.g., radioimmunotherapy with alpha particles) [51, 52].

Jurcic et al. were the first group which started the clinical experiences on the humankind in 1996. They used RIC consisting of 213Bi and HuM195 antibody for acute myelogenous leukemia patients. The results showed a temporary reduction in the number of leukemia cells presented in the blood flow. Moreover, it reported that the dose of cancerous cells is 10 to 40 thousand times larger than sound cells.

Nilsson et al. performed the phase I of Alpharadin (223Ra) investigatin in patients of bony metastasis of prostate and breast cancers and showed that remedial doses will not lead to blood poisoning [53-63].

Allen et al. investigated the performance of RIC consisting of 213Bi and 9,2,27 antibodies for melanoma patients in IV level which have secondary hypodermic melanoma and demonstrated its clinical response. In addition, it found that kidney has received the highest dose among the organs [64-69].

Schmidt et al. performed the phase I of clinical experience for investigating of limiting doses in remediation of non-Hodgkin's lymphoma with 213Bi. Their drug targeted by CD33 and CD20 antibodies and labeled for imaging by 111In. The preliminary obtained results have not shown a considerable receiving of drug in other organs but light leucopenia has shown in two patients [70-75].

An interesting note in these studies is that 213Bi is the first alpha emitter radionuclide which is clinically studied due to its simple availability via 225Ac-213Bi generator. However, numerous studies are under performing in research centers which investigate the possibility of using other alpha emitter radionuclides for cancer remediation. An investigation about the use of 212Pb liposomal (which 212Pb is transformed to 212Bi) in ovary cancer remediation is under consideration in Algeta Corporation in Norway. In addition, use of 211At in Duke University, 212Bi for melanoma remediation in University of Missouri and 210Po in University of Maryland Consortium are under study [76-85].

3 Conclusion

It seems that the radioimmunotherapy with alpha particles, which have high LET and low range, for controlling of metastatic diseases, hematologic malignancies such as various types of leukemia and lymphoma and local remedies of cancer such as intraperitoneal remedy or intra-arterial liver are very suitable. Among the suitable radioisotopes for remedial actions, although 149Tb make the highest poisoning, 213Bi is the best option due to its availability via 225Ac-213Bi generator. The pharmacokinetic and dosimetry studies of RICs for estimating the biological effects of radiation are necessary and because of the short range of alpha particles and high LET, studying of biological effects in microdosimetry approach will be valuable. In addition to 213Bi which performs well in most of previous clinical experiences for various diseases, the clinical experience of this method is performing in several research centers to examine the other radionuclides with various MAbs

and it hopes that new drugs will be supplied to the market up to the end of current decades. Finally, it seems that the most important obstacle for performing of this new remedial and promising method in the country is unavailability of alpha emitter radioisotopes. However, it must be hopeful to reach the producing technology of these isotopes by native researchers in the future.

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