Marmara Medical Journal (2013) 26:1-4
DOI: 10.5472/MMJ.2012.02630.1

REVIEW / DERLEME

Nanotechnology in the field of clinical oncology

Klinik onkoloji alanında nanoteknoloji

Mehmet Rıfkı TOPÇUL, İdil ÇETİN

ABSTRACT

Surgery, radiotherapy and chemotherapy are conventional methods used in cancer treatment. Because these methods have some limitations, it is difficult to cure the disease completely. In recent years, to overcome these limitations and also to increase the efficiency of the therapies, new methods are being developed. In this context, nanotechnology is a promising approach. Therefore, cancer nanotechnology has become an important field. Some applications used in the field of cancer nanotechnology include novel nanodrugs that decrease the adverse effects of conventional cancer drugs and increase their therapeutic efficacy, gold nanoparticles which increase the sensitivity to radiotherapy and nanoparticles used in thermal ablation therapy among many others.

Key words: Oncology, Cancer, Nanotechnology, Nanodrug, Radiotherapy, Hyperthermia

ÖZET

Cerrahi, radyoterapi ve kemoterapi kanser tedavisinde kullanılan geleneksel yöntemlerdir. Bu yöntemlerin bazı sınırlamaları olduğu için hastalığı tamamen tedavi etmek güçtür. Son yıllarda bu sınırlamaların üstesinden gelmek ve aynı zamanda tedavi etkinliğini arttırmak için yeni yöntemler geliştirilmektedir. Bu bağlamda nanoteknoloji umut verici bir yaklaşımdır. Bu nedenle kanser nanoteknolojisi dikkat çekici bir alan haline gelmiştir. Geleneksel kanser ilaçlarının yan etkilerini azaltan ve tedavi etkinliğini arttıran yeni nano ilaçlar, radyoterapiye duyarlılığı arttıran altın nano partiküller ve termal ablasyon tedavisinde kullanılan nano partiküller kanser nanoteknolojisi alanında kullanılan uygulamalardan sadece bazılarıdır.

Anahtar kelimeler: Onkoloji, Kanser, Nanoteknoloji, Nanoilaç, Radyoterapi, Hipertermi

Mehmet Rıfkı Topçul (✉)
Biology Department, Faculty of Science, İstanbul University, İstanbul, Turkey.
E-mail*: topcul@istanbul.edu.tr*

İdil Çetin
Radiobiology Department, Intitute of Science , Istanbul University, İstanbul,Turkey.

Submitted/Gönderilme: 20.11.2012 - **Accepted/Kabul:** 13.12.2012

Introduction

Clinically, cancer is defined as a large number (up to a hundred) of complex diseases that behave differently depending on the cell types from which they originate. Cancers vary in age of onset, growth rate, invasiveness, prognosis, and responsiveness to treatment [1]. The most common cancer treatments are limited to chemotherapy, radiation, and surgery. Frequent challenges encountered by current cancer therapies include the nonspecific systemic distribution of antitumor agents, inadequate drug concentrations reaching the tumor, and the limited ability to monitor therapeutic responses. Poor drug delivery to the target site leads to significant complications, such as multidrug resistance [2]. Nowadays to overcome all these limitations in the treatment of cancer, researchers have started working on nanotechnological applications in the field of clinical oncology.

Nanotechnology can be defined simply as the technology at the scale of one-billionth of a metre. It is the design, characterization, synthesis and application of materials, structures, devices and systems by controlling shape and size at the nanometre scale [3]. Nanomedicine is defined as the application of nanobiotechnology to medicine and is based on the use of nanoscale materials and devices for diagnosis and drug delivery as well as for the development of advanced pharmaceuticals referred to as nanopharmaceuticals [4].

In this review, some nanodrugs, which can both increase the effectiveness and reduce side effects of cancer treatment, increasing the effectiveness of radiation therapy with gold nanoparticles and the application of hyperthermia through the nanomaterials are discussed.

Chemotherapy based on nanotechnology

Most current anticancer agents do not differentiate between cancerous and normal cells, leading to systemic toxicity and adverse effects. This greatly limits the maximum allowable dose of the drug. In addition, rapid elimination and widespread distribution into targeted organs and tissues requires the administration of a drug in large quantities, which is not economical and often results in undesirable toxicity [5]. Techniques for controlled drug delivery represents one of the frontier areas of science, which involves multidisciplinary

scientific approaches that can contribute to human health care. These delivery systems offer numerous advantages compared to conventional dosage forms, including improved efficacy, reduced toxicity, and improved patient compliance and convenience [6].

The new generation of nanotechnology-based drug formulations is challenging the accepted ways of cancer treatment. Multi-functional nanomaterial constructs have the capability to be delivered directly to the tumor site and eradicate cancer cells selectively, while sparing healthy cells. Tailoring of the nano-construct design can result in enhanced drug efficacy at lower doses that can free drug treatment, can produce a wider therapeutic window, and lower side effects. Nanoparticle carriers can also address several drug delivery problems that could not be effectively solved in the past, including reduction of multi-drug resistance effects, delivery of small interfering RNA (siRNA), and penetration of the blood-brain-barrier. Although challenges in understanding toxicity, biodistribution, and in paving an effective path for regulating the actions of the nanoscale devices carry a vast promise to change ways cancer is diagnosed and treated [7]. The design of a universal nanotechnology formulation with chemotherapeutic agents is crucial. A successful formulation, one that acts as a good therapeutic carrier for cancer therapies, would exhibit the following features: (i) it would be stable in the physiological environment, (ii) have a longer circulation life time than currently available treatments, (iii) avoid opsonization and processing by the reticuloendothelial system (RES), (iv) promote endocytosis, and (v) enhance tumor uptake. The specificity of these formulations can be further enhanced by the conjugation of antibodies to the nanoformulations and these immunoconjugated formulations will have a better therapeutic efficacy than other drug formulations [8].

Albumin Bound Paclitaxel

Taxanes are a class of chemotherapy agents that promote the polymerization of tubulin into highly stable, intracellular microtubules. These microtubules cause cell death by interfering with normal cell division. The first taxane developed and tested in the field of oncology was paclitaxel [9]. Paclitaxel is a naturally occurring complex product extracted from the bark of the Western yew (*Taxus brevifolia*) and is widely used for the treatment of breast, lung, and advanced ovarian cancer [10-12]. Advances in the use of taxanes clinically have been limited by their chemical formulation: they are highly hydrophobic molecules. To overcome this poor water solubility, lipid-based solvents are used as a vehicle. Solubility of paclitaxel is enhanced with a mixture of 50:50 Cremophor EL® (CrEL, a non-ionic surfactant polyoxyethylated castor oil; BASF, Florham Park, NJ, USA) and ethanol (Taxol® and generic equivalents) [13]. The solvent Cremophor-EL used in formulations of paclitaxel causes acute hypersensitive reactions. To reduce the risk of allergic reactions when receiving paclitaxel, patients must undergo pre-medication using steroids and anti-histamines and be given the drug using slow infusions lasting a few hours [14]. In order to overcome insolubility problems, albumin bound paclitaxel was developed. This drug is the only example of a regulatory approved (FDA, USA) nanoparticle formulation for intravenous drug delivery in cancer patients. It is paclitaxel bound to albumin nanoparticles, with a mean diameter of 130 nm, for use in individuals with metastatic breast cancer who have failed a combination chemotherapy or relapsed within 6 months of adjuvant chemotherapy [15, 16]. This formulation overcomes poor solubility of paclitaxel in the blood and allows patients to receive 50% more paclitaxel per dose over a 30-min period [17]. Because it is solvent-free solvent related toxicities are also eliminated [14].

Liposomal Doxorubicin

Anthracyclines are an important class of antitumor agents with significant biological activities. Anthracyclines are DNA intercalating agents, which can bind to DNA. These agents bind to specific DNA sequences, form topoisomerase-DNA complexes, and cause double strand DNA breaks. Anthracycline is a Doxorubicin that is an essential component of treatment of breast cancer, childhood solid tumors, and soft tissue sarcomas [18, 19) . Although anthracyclines are used in many types of cancer, they have cardiotoxic effects. Acute cardiotoxicity may manifest as nonspecific ST-segment and T-wave abnormalities. In contrast to early effects, late anthracycline cardiotoxicity is cumulative, dose related, and, at sufficiently high dosages, can result in congestive heart failure (CHF) and left ventricular (LV) dysfunction [20]. Doxorubicin is recognized as one of the most active drugs for breast cancer, but its clinical utility is limited because of a cumulative dose-dependent cardiac myopathy that can lead to potentially fatal congestive heart failure [21-24].

The mechanism of doxorubicin-induced cardiotoxicity involves the formation of a stable complex of drug with ferric iron, and this reacts with oxygen, forming superoxide anions, hydrogen peroxide, and hydroxyl radicals. These free radicals cause lipid peroxidation. The injury is initially subclinical, but continued treatment results in progressive myocyt damage leading to cumulative dose-dependent cardiac dysfunction that can manifest during therapy, months after the last anthracycline dose or even years later [25]. In an effort to minimize anthracycline-induced cardiotoxicity, a liposome-encapsulated doxorubicin (Myocet™, St. Mary's Pharmaceutical Unit, Quadrant Centre, Cardiff Business Park, Llaninishan, Cardiff Wales; Trade Company, Cephalon Europe, Maison Alfort, France) has been developed [26]. Liposomal doxorubicin is approximately 190 nm in size and was approved by the European Agency for the Evaluation of Medicinal Products (EMEA) in 2000 for the treatment of metastatic breast cancer [17]. The formulation consists of encapsulation of the water-soluble doxorubicin within a phospholipid membrane to prevent doxorubicin from

exiting the circulation through capillary junctions in healthy tissues. However, liposome-encapsulated drug appears to pass easily through the damaged capillaries of tumor tissues [26]. Therefore, liposomal encapsulation of doxorubicin is designed to increase safety and tolerability by decreasing cardiac and gastrointestinal toxicity through decreased exposure of these tissues to doxorubicin, while effectively delivering the drug to the tumor [27].

Nanotechnology-based radiotherapy

Radiotherapy involves the use of high-energy rays to kill cancer cells [28]. Treatment depends upon the sensitivity of dividing cells being destroyed by X-rays or gamma rays emitted from a radioactive source [29]. Here, the ionizing radiation presents the advantage of penetrating tissues, which allows the treatment of deeply sited tumors [30]. However, radiotherapy has the disadvantage of causing some damage to normal tissues and cells covering and surrounding the cancer in the irradiated treatment area [29]. One major difficulty is the lack of selectivity between the tumor and the healthy surrounding tissue. The implementation of such techniques is therefore limited by the tolerance of normal tissues. The challenge of future radiation therapies is to develop methods for targeting the dose deposition to tumors and to enhance the biological effects [30].

Chemical radiosensitizers have been developed to increase the sensitivity of tumor cells' to radiation by targeting numerous different biochemical pathways, including targeting of hypoxic cells, suppression of radioprotective thiols, and inhibition of DNA repair [31-34]. Although these applications have shown promise in one or more areas, they are generally toxic to normal tissues, have uncertain radiosensitizing mechanisms, and sometimes rely on a sub-cellular target that is subject to change. It has been concluded that the synergistic gain from these chemical radiosensitizers has been marginal [35].

Enhancement of the radiation dose by high atomic number (Z) materials has long been of interest [36]. It has been reported that loading high Z materials into the tumor could result in greater photoelectric absorption within the tumor than in surrounding tissues, and thereby enhance the dose delivered to a tumor during radiation therapy [36, 37]. Among other nanoparticle systems, gold nanoparticles have been explored as radiosensitizers [38]. While most of the research in this area has focused on either gold nanoparticles with diameters of less than 2 nm or particles with micrometer dimensions, it has been shown that nanoparticles 50 nm in diameter have the highest cellular uptake [39]. Gold nanoparticles have properties that make them attractive for use in cancer therapy including their small size, biocompatibility, and passive accumulation in tumors because of the enhanced permeability and retention effect [40]. In addition to these properties gold nanoparticles are capable of forming reactive oxygen species when irradiated [41].

The results suggest that the enhancement of radio sensitivity is due to the production of additional low-energy secondary electrons caused by the increased absorption of ionizing radiation energy by the metal of gold nanoparticles or of a thick gold substrate. Since short-range low-energy secondary electrons are produced in large amounts by any type of ionizing radiation, and since on average only one gold nanoparticle per DNA molecule is needed to increase damage considerably, targeting the DNA of cancer cells with gold nanoparticles may offer a novel approach that is generally applicable to radiotherapy treatments [42].

Nanotechnology-based thermal ablation therapy

Thermal ablation therapy (hyperthermia) is defined as a therapy in which tumor temperature is raised to values between 41°C and 45°C by external means. It can be applied locally/regionally or to the whole body depending from the stage of the cancer in patients For decades hyperthermia has been an area of laboratory investigation [43]. Hyperthermia therapy is the most promising of these methods but is limited by incomplete tumor destruction and damage to adjacent normal tissues. The radiofrequency ablation technique currently used, is a type of interstitial hypothermia that requires invasive needle placement and is limited by the accuracy of the targeting. Use of nanoparticles has refined noninvasive thermal ablation of tumors, and several nanomaterials have been used for this purpose. These include gold nanomaterials, iron nanoparticles, magnetic nanoparticles, carbon nanotubes and affisomes. Heating of the particles can be induced by magnets, lasers, ultrasound, photodynamic therapy or low-power X-rays [4]. Perhaps the most researched property of carbon nanotubes for cancer therapy in recent years has been their strong absorbance in the near-infrared light range (700–1400 nm). This property makes carbon nanotubes an enticing vehicle for selective cell killing because many biological tissues are transparent in the near-infrared range. It is well documented that carbon nanotubes themselves are not toxic to cells but, when combined with near-infrared light therapy, they have been shown to cause cell death by hyperthermia [44].

Conclusions

Currently cancer is a disease that cannot be cured completely. Conventional therapies cannot target cancer cells exclusively. In addition to cancer cells, normal healthy cells are affected by these therapies. For this reason these therapies have some limitations. To overcome these limitations, new methods are being developed. Adaptation of nanotechnology in the field of oncology includes these new methods.

Nowadays, nanotechnology based methods are applied in many fields of clinical oncology. Limitations in the treatment of cancer will be eliminated with the development and application of these methods. For this reason nanotechnological approaches are seen as promising developments in clinical oncology.

References

1. Klug WS, Cummings MR, Spencer CA, Palladino MA. Cancer and regulation of the cell cycle. In: Klug WS, Cummings MR, Spencer CA, Palladino MA, editors. Concept of Genetics. San Francisco: Pearson, 2009; 511-30.
2. Wang X, Yang L, Chen Z, Shin DM. Application of nanotechnology in cancer therapy and imaging. CA Cancer J Clin 2008; 58:97–110. doi:10.3322/CA.2007.0003
3. Ochekpe NA, Olorunfemi PO, Ngwuluka NC. Nanotechnology and drug delivery part 1: background and applications. Trop J Pharm Res 2009; 8: 265-74. doi:10.4314/tjpr.v8i3.44546
4. Jain KK. Advances in the field of nanooncology. BMC Medicine 2010; 8: 83. doi:10.1186/1741-7015-8-83
5. Sinha R, Kim GJ, Nie S, Shin DM. Nanotechnology in cancer therapeutics: bioconjugated nanoparticles for drug delivery. Mol Cancer Ther 2006; 5: 1909-17. doi:10.1158/1535-7163.MCT-06-0141
6. Kumar MNVR. Nano and microparticles as controlled drug delivery devices. J Pharm Pharmaceut Sci 2000; 3:234-58.
7. Farrell D, Ptak K, Panaro NJ, Grodzinski P. Nanotechnology-based cancer therapeutics-promise and challenge-lessons learned through the NCI alliance for nanotechnology in cancer. Pharm Res 2011; 28: 273-8. doi:10.1007/s11095-010-0214-7
8. Yallapu MM, Jaggi M, Chauhan SC. Scope of nanotechnology in ovarian cancer therapeutics. J Ovarian Res 2010; 3:1-10. doi:10.1186/1757-2215-3-19
9. Cella D, Peterman A, Hudgens S, Webster K, Socinski MA. Measuring the side effects of taxane therapy in oncology the functional assessment of cancer therapy–taxane (FACT-Taxane). Cancer 2003; 98: 822-31.
10. Rowinsky EK, Donehower RC. Paclitaxel (Taxol). N Engl J Med 1995; 332: 1004-14.
11. Spencer CM, Faulds D. Paclitaxel: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential in the treatment of cancer. Drugs 1994; 48: 794–847. doi:10.2165/00003495-199448050-00009
12. Onetto N, Canetta R, Winograd B, et al. Overview of paclitaxel safety. J Natl Cancer Inst Monogr 1993;15:131–9.
13. Miele E, Spinelli GP, Miele E, Tomao F, Tomao S. Albumin-bound formulation of paclitaxel (Abraxane® ABI-007) in the treatment of breast cancer. Inter J Nanomed 2009; 4: 99-105.
14. Suri SS, Fenniri H, Singh B. Nanotechnology-based drug delivery systems. J Occup Med Toxicol 2007; 2: 1-6. doi:10.1186/1745-6673-2-16
15. Bartels CL, Wilson AF. How does a novel formulation of paclitaxel affect drug delivery in metastatic breast cancer? US Pharm 2004; 29 : 18-23.
16. Garber K. Improved paclitaxel formulation hints at new chemotherapy approach. J. Natl Cancer Inst 2004; 96 : 90-1. doi:10.1093/jnci/96.2.90
17. Moghimi SM. Passive targeting of solid tumors: Pathophysiological principles and physicochemical aspects of delivery systems. In: Amiji MM, editor. Nanotechnology for Cancer Therapy. ABD: CRC Press, 2007: 11-8.
18. Barrón-Vivanco B, Rothenberg S, Medina-Díaz I, et al. AKRs expression in peripheral blood lymphocytes from smokers : The role of body mass index. Hum Exp Toxicol 2012 Ahead of print. doi: 10.1177/0960327112455071
19. Preobrazhenskaya MN, Tevyashova AN, Olsufyeva EN, Huang KF, Huang HS. Second generation drugs-derivatives of natural antitumor anthracycline antibiotics daunorubicin, doxorubicin and carminomycin. J Med Sci 2006; 26: 119-28.
20. Yeh ETH, Tong AT, Lenihan DJ, et al. Cardiovascular complications of cancer therapy diagnosis, pathogenesis, and management. Circulation 2004; 109: 3122-31. doi: 10.1161 /01.CIR.0000133187.74800.B9
21. Doroshow JH. Effect of anthracycline antibiotics on oxygen radical formation in rat heart. Cancer Res 1983; 43: 460-72.
22. Rajagopalan S, Politi PM, Sinha BK, Myers CE. Adriamycin-induced free radical formation in the perfused rat heart: Implications for cardiotoxicity. Cancer Res 1988; 48: 4766-9.
23. Jackson JA, Reeves JP, Muntz KH, et al. Evaluation of free radical effects and catecholamine alterations in adriamycin cardiotoxicity. Am J Pathol 1984; 117:140-53.
24. Myers CE, McGuire WP, Liss RH, Ifrim I, Grotzinger K, Young RC. Adriamycin: The role of lipid peroxidation in cardiac toxicity and tumor response. Science 1977; 197: 165-7. doi:10.1126/science.877547
25. Batist G, Ramakrishnan G, Rao CS, et al. Reduced cardiotoxicity and preserved antitumor efficacy of liposome-encapsulated doxorubicin and cyclophosphamide compared with conventional doxorubicin and cyclophosphamide in a randomized, multicenter trial of metastatic breast cancer. J Clin Oncol 2001; 19: 1444-54.
26. Poletti P, Bettini AC, Caremoli ER, Labianca R, Tondini C. Liposomal-encapsulated doxorubicin (Myocet™; D-99) and vinorelbine in previously treated metastatic breast cancer patients: a feasibility study. Tumori 2008; 94: 686-90.
27. Mross K, Niemann B, Massing U, et al. Pharmacokinetics of liposomal doxorubicin (TLC-D99; Myocet) in patients with solid tumors: an open-label, single-dose study. Cancer Chemother Pharmacol 2004; 54: 514-24. doi:10.1007/s00280-004-0825-y
28. Thackery E, (editor). The Gale Encyclopedia of Cancer. London: Gale Group, Thomson Learning, 2002.
29. Stephens FO, Aigner KR. Targeting cancer. In: Stephens FO, Aigner KR, editors. Basics of Oncology. London-New York: Springer, 2009: 87-120.
30. Porcel E, Liehn S, Remita H, et al. Platinum nanoparticles: a promising material for future cancer therapy? Nanotechnology 2010; 21: (085103) 1-7. doi:10.1088/0957-4484/21/8/085103
31. Brown JM, Wilson WR. Exploiting tumour hypoxia in cancer treatment. Nat Rev Cancer 2004; 4 :437–47. doi:10.1038/nrc1367
32. Minchinton AI, Rojas A, Smith KA, et al. Glutathione depletion in tissues after administration of buthionine sulphoximine. Int J Radiat Oncol 1984; 10: 1261–4. doi:10.1016/0360-3016(84)90329-8
33. Eberhardt W, Pottgen C, Stuschke M. Chemoradiation paradigm for the treatment of lung cancer. Nat Clin Pract Oncol 2006; 3: 188–99. doi:10.1038/ncponc0461
34. Hao D, Ritter MA, Oliver T, Browman GP. Platinum-based concurrent chemoradiotherapy for tumors of the head and neck and the esophagus. Semin Radiat Oncol 2006; 16: 10–9. doi: 10.1016/j.semradonc.2005.08.002
35. Wang L, Yang W, Read P, Larner J, Sheng K. Tumor cell apoptosis induced by nanoparticle conjugate in combination with radiation therapy. Nanotechnology 2010; 21: (475103) 1-7. doi:10.1088/0957-4484/21/47/475103
36. Chang MY, Shiau AL, Chen YH, Chang CJ, Chen HH, Wu CL. Increased apoptotic potential and dose-enhancing effect of gold nanoparticles in combination with single-dose clinical electron beams on tumor-bearing mice. Cancer Sci 2008; 99: 1479–84. doi:10.1111/j.1349-7006.2008.00827.x
37. Misra R, Acharya S, Sahoo SK. Cancer nanotechnology: application of nanotechnology in cancer therapy. Drug Discov Today 2010; 15: 842- 50. doi:10.1016/j.drudis.2010.08.006
38. Butterworth KT, McMahon SJ, Currell FJ, Prise KM. Physical basis and biological mechanisms of gold nanoparticle radiosensitization. Nanoscale 2012; 4 : 4830-8.
39. Chithrani DB, Jelveh S, Jalali F, et al. Gold nanoparticles as radiation sensitizers in cancer therapy. Radiat Res 2010; 173: 719-28. doi:10.1667/RR1984.1
40. Jain S, Coulter JA, Hounsell AR, et al. Cell-specific radiosensitization by gold nanoparticles at megavoltage radiation energies. Int J Radiat Oncol 2011; 79: 531-9. doi:10.1016/j.ijrobp.2010.08.044
41. Geng F, Song K, Xing JZ, et al. Thio-glucose bound gold nanoparticles enhance radio-cytotoxic targeting of ovarian cancer. Nanotechnology 2011; 22: (285101) 1-8. doi:10.1088/0957-4484/22/28/285101
42. Zheng Y, Hunting DJ, Ayotte P, Sanche L. Radiosensitization of DNA by gold nanoparticles irradiated with high-energy electrons. Radiat Res 2008; 169: 19-27. doi:10.1667/RR1080.1
43. Baronzio GF, Hager ED. Preface. In: Baronzio GF, Hager ED, editors. Hyperthermia in Cancer Treatment: A primer. USA: Springer Science, 2006: 135.
44. Prickett WM, Rite BDV, Resasco DE, Harrison RG. Vascular targeted single-walled carbon nanotubes for near-infrared light therapy of cancer. Nanotechnology 2011; 22: 1-7. doi:10.1088/0957-4484/22/45/455101