Diminishing the Side Effects of Cancer Treatment by Improving Treatment Delivery

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ABSTRACT

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Cancer is one of the leading causes of death in the world and is expected to become more prevalent each year. Cancer is caused by the uncontrollable growth of cells within the human body. This excessive growth can lead to the formation of malignant tumors, which invade parts of the body. Currently, the most common approach to treating cancer is surgery, chemotherapy, and radiation treatment. However, chemotherapy and radiation can cause drastic, harmful side effects to patients because they not only affect cancer cells, but normal proliferative cells as well. In many cases, a particular chemotherapy is avoided because the risks of side effects greatly outweigh the effect of the drug on the tumor. Therefore, if adverse effects are going to be eliminated and cancer treatment optimized, tumor cells must be specifically targeted and normal cells spared. One method of generating tumor specificity in cancer treatment that has recently gained interest and optimism is the use of medical devices. As technology has improved, the possibilities and applications of medical devices have become nearly limitless. In cancer treatment, medical devices can guide their cargo, whether it is a drug or radiation, directly to tumor sites within the patient. As a result, adverse effects should be diminished and cancer treatment should be optimized.

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Introduction

Cancer is a troubling, deadly disease that has been affecting people for centuries. Cancer involves the uncontrollable growth of cells in the body, forming tumors (1). In 2008, cancer was a leading cause of death (13% of deaths) in the world (2). There are over 200 types of cancer and many facts are still unknown about the disease. Treatment options and effectiveness has significantly grown and improved over the years, especially recently; however, one common theme among cancer treatments is the incidence of adverse effects. Even though tumors may be eliminated after surgery or shrunk immediately after chemotherapy, the health and well-being of patients are affected by conditions such as nausea, hair loss, infection, anemia, nerve problems, urinary problems, and many others (3). Furthermore, many potential cancer treatments that can have curative implications do not even receive FDA (Food and Drug Administration) approval because of the severity of their side effects compared to their effect on the tumor (4). The incidence of side effects can be explained by the current, common approach of treating cancer. Proliferating cells are targeted by small molecules, antibodies, radiation, or other compounds, usually causing apoptosis, or cell death. However, tumor cells are not the only proliferating cells in the body of a cancer patient. Normal, noncancerous proliferating cells, such as blood cells, hair cells, and cells that line the digestive system, are also unintentionally targeted by cancer treatments, leading to the adverse effects previously mentioned. This realization highlights the importance of improving treatment delivery so that only cancerous cells are targeted, sparing normal cells and diminishing adverse effects. One area of research that has gained much attention bridges biology and

engineering to generate medical devices which can be used to direct cancer treatments, such as chemotherapy and radiation, to desired locations within patients.

With modern technology, medical devices are involved in almost every aspect of the medical field and are responsible for saving countless lives. Medical devices have been used for many years, including the scalpels used for the first surgeries and syringes that delivered the first vaccines. However, medical devices only started being regulated, similar to drugs, in the 1970s as they became more advanced and medically influential (5). According to the FDCA (Federal Food, Drug, and Cosmetic Act), a medical device is:

> "An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is
>
> 1. Recognized in the official National Formulary or the United States Pharmacopeia, or any supplement to them,
> 2. Intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
> 3. Intended to affect the structure or any function of the body of man or other animals, and
>
> which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes." (5)

Therefore, medical devices include a wide variety of instruments with varying applications that can range from operating room monitors to contact lenses to sunscreen. The vast potential of medical devices illustrates the importance it can have in treatment delivery. For example, rather than administer a drug or radiation alone, a medical device, that can be injected or implanted, can be designed to deliver the treatment at particular times and/or locations. Since the medical device is expected to provide precise delivery,

normal cells can be avoided, diminishing side effects. Medical devices that exhibit these properties are either practiced in the medical field or being developed and tested today (6-10). Among these, radiation seeds, which can be delivered in specific locations, are being used that proximally emit radiation to tumor cells (6). Balloon catheters also deliver localized radiation to tumors, but can be used in hard-to-treat regions such as the brain (7). Nanoparticles and carbon nanotubes that encase or carry a desired therapeutic compound have been constructed in a manner that only or mainly cancerous cells receive treatment (8, 9). Implantable microelectromechanical systems (MEMS) are currently being designed that can locally deliver anticancer agents to tumors at a controllable time, rate, and dosage (10). The promising capabilities of these examples suggest that medical devices may be the key to improving treatment delivery in cancer patients so that normal cells are unharmed and adverse effects are either eliminated or reduced.

Radiation Seeds

Several medical devices have arisen for cancer treatment that can deliver radiation. Radiation seeds are extremely small medical devices (about 20-60 micrometers), usually spherical or rod-shaped, that contain radioactive material and can be permanently injected into cancer patients (11). This type of internal radiation therapy is called permanent brachytherapy (11). The seeds are injected into a specific area of the body where they can highly localize near tumor cells and emit radiation. The emitted radiation causes DNA damage of the tumor cells, and eventually apoptosis (11). SIR spheres are radiation seeds that were approved by the FDA in 2002 as medical devices for the treatment of liver cancer (11). They are resin microspheres that contain the radioisotope Yttrium-90 and are delivered and embolized into the hepatic artery, which is the main blood source of liver tumors, delivering close-range radiation directly to tumor cells (12). Pre-approval clinical trials showed that patients receiving SIR spheres combined with chemotherapy had significantly higher survival rates than patients receiving chemotherapy alone (29.4 months vs. 12.8 months) (13). Similar to SIR spheres, Theraspheres are radiation seeds that are indicated for liver cancer treatment and contain Yttrium-90; however, the microspheres are made out of glass rather than resin (14). Other radiation seeds that contain the radioisotope Iodine-125 or Palladium-103 have been used to treat prostate cancer by injecting them directly into the prostate. Radiation seeds remain inside the patient, but brachytherapy ceases after the radiation has decayed (15). Long-term clinical trials testing these radiation seeds showed that disease-free survival ranged from 66% to 87% of prostate cancer patients after an average of 10

years (16). Radiation seeds offer several advantages over standard, external radiation therapy that can not only lead to fewer normal cells being harmed, but also stronger doses of radiation being delivered to the tumors.

Conventional radiation therapy involves exposing specific areas of the body of a patient to external radiation to kill cancer cells within. However, many healthy, dividing cells are also subjected to the radiation treatment, causing unsettling side effects. For example, nausea and vomiting occur if the stomach or abdomen is exposed to the radiation treatment and infertility can occur if the gonads are exposed. In addition, external radiation must bypass many layers of healthy tissue to reach the tumor cells, minimizing the strength and effectiveness of the treatment (17). Radiation seeds can solve these problems by providing internal treatment delivery rather than non-specific external radiation. Radiation seeds are injected either directly into tumors or in areas that would lead to selective tumor localization. Therefore, the majority of radiation is directed towards tumor cells and many normal cells and tissues are avoided. For example, SIR spheres and Theraspheres intend to evade damage to normal cells and side effects by inserting the seeds into the hepatic artery. Since normal liver cells mainly receive blood from portal circulation, and tumor cells from the hepatic artery, the overwhelming majority of radiation should be delivered to tumor cells (12). Another advantage is that the radiation does not have to bypass many layers of healthy tissue to reach the tumor. This not only spares additional normal cells and tissues from receiving radiation, but also strengthens the effects of radiation on tumor cells. After injection, the proximity of the radiation seeds to the tumor allows for close-range, high-levels of radiation delivery. Higher levels of radiation have stronger therapeutic results, so the tumor cells shrink or

are eliminated more effectively. For example, clinical trials showed that Iodine-125 and Palladium-103 radiation seeds provided significantly higher progression-free survival in prostate cancer patients compared to conventional radiation therapy (18). In addition, these radiation seeds showed a lower risk of adverse effects (18). Current research and trials have tested permanent Cesium-131 radiation seeds for prostate cancer treatment. Results of the clinical trials have shown that these radiation seeds combat highly proliferative cells even better than Iodine-125 and Palladium-103 radiation seeds, with similar safety (15). Therefore, radiation seeds can potentially have fewer side effects than conventional radiation therapy and combat tumors more strongly as well. Furthermore, if tumors can be eliminated more effectively, than fewer treatments, and consequently fewer opportunities to harm normal cells, would be necessary to care for patients.

Clinical trials have illustrated the implications radiation seeds can have on not only eliminating tumors, but preventing recurrence as well. Cancer recurrence is the return of cancer after treatment noticeably eliminated all tumor cells in the body (19). In one clinical trial, radiation seeds containing Phosphorous-32 were used to prevent recurrence in liver cancer patients that had already undergone hepatectomy, partial surgical removal of the liver. The results of the clinical trials demonstrated that recurrence rates significantly decreased and overall survival at three years increased in about 65 % of patients (20). In addition, after three years, no significant side effects were observed that would normally occur from the systemic radioactive absorption associated with conventional radiation therapy (20). These findings suggest that radiation seeds can have significant implications in reducing the possibility of side effects. Since the incidence of recurrence would require patients to undergo additional treatments, the

chance that the normal cells of a patient would be affected by chemotherapy or radiation also increases. This forces patients to endure more side effects or experience side effects that were previously avoided. Therefore, by preventing recurrence, radiation seeds such as Phosphorous-32 can greatly minimize the amount of side effects cancer patients potentially experience. Implanting radiation seeds can possibly become a standard procedure in cancer treatments that involve surgery. After tumors have been surgically removed, radiation seeds can be implanted before ending the surgery to prevent recurrence. Additionally, this would allow the radiation seeds to be positioned in the exact locations desired by the oncologist, further diminishing the chances of side effects from systemic radioactive absorption. The advantages of fewer side effects, more effective tumor elimination, and recurrence prevention may lead to a future where radiation seeds have replaced external radiation as the conventional radiation therapy for cancer patients.

Balloon Catheters

Other medical devices, such as balloon catheters, have also shown promise in being able to diminish side effects by locally delivering radiation to tumors. Balloon catheters are medical devices that comprise a tube with an inflatable balloon that can be inserted into cavities or ducts within the body (21). The inflatable balloon allows the desired region to be expanded to create space between the tissue and the substance being delivered (21). In cancer treatment, balloon catheters are used as a form of temporary brachytherapy. The balloon catheter is inserted into a cavity formed by surgical tumor removal to release close-range radiation to tumor cells (21). After each daily treatment, the catheter can be unplugged from the radiation source so that patients can carry out normal activities (21). Once brachytherapy is completely finished, the balloon is deflated and the catheter is removed (21). An example of a balloon catheter is the GliaSite Radiation Therapy System (GliaSite RTS), which is approved for the treatment of brain cancer. After a brain tumor has been surgically removed, the GliaSite RTS catheter is inserted into the region and delivers liquid Iodine-125. After less than a week of treatment, the catheter is completely removed (7). Another balloon catheter, the MammoSite, received FDA approval in 2002 for breast cancer treatment (22). The Mammosite is inserted into the cavity formed by tumor removal and delivers high-dose radiation seeds. The radiation seeds are removed after each daily treatment and the catheter is removed after the entire treatment is finished, which takes about five days (22). Other balloon catheters have been used for breast cancer treatment as well, such as SAVI and ClearPath (23). The localized delivery of balloon catheters offers several

advantages over conventional radiation therapy, such as harming fewer normal cells and decreasing treatment time for patients.

Similar to radiation seeds, since balloon catheters are inserted into a precise cavity and the radiation is delivered internally, side effects can be significantly diminished compared to conventional radiation therapy because fewer normal cells are exposed to radiation. For example, after five years of observation, a clinical trial showed that MammoSite treated patients as effectively as conventional radiation therapy and only showed severe side effects (infection) in about 9 % of patients (24). Another advantage is that balloon catheter treatment only takes a few days, while conventional radiation therapy takes about six to seven weeks (21, 22). Since each additional day a patient is exposed to radiation therapy is another opportunity that normal cells can be harmed, fewer treatment days can potentially save patients from experiencing side effects. Additionally, fewer treatment days improves patient quality of life by decreasing the time and stress involved with constantly receiving cancer treatment. Balloon catheters may not combat tumors as strongly as permanent radiation seeds, but they diminish the incidence of adverse effects just as well. Furthermore, the temporary nature of balloon catheters allows them to be used in regions that are not suitable for radiation seeds, such as the brain (radiation seeds have not been proven safe and effective in the brain) (25). The successful local deliverability of balloon catheters suggests that they can be used to deliver other substances besides radiation, such as anticancer drugs, to tumor sites.

If balloon catheters are capable of delivering radiation and chemotherapy to tumors, than the two main causes of cancer treatment side effects can be addressed. In 2009, the FDA gave market clearance to IsoFlow, a balloon catheter that can deliver

anticancer drugs (26). Just like with radiation, the catheter would be inserted into a region that allows local delivery of the drug to tumor sites. This would avoid many of the adverse effects that occur from the anticancer drug affecting normal cells (26). One can understand how balloon catheters such as IsoFlow can immensely improve the safety and efficacy of cancer treatments. For example, Avastin is an anticancer drug approved for the treatment of several cancers. Avastin prevents angiogenesis, the formation of new blood vessels. Angiogenesis is a common aspect of tumor cells and is necessary for their growth (27). However, since Avastin is orally delivered and non-specific, problems can arise in normal processes that involve the circulatory system. Patients receiving Avastin can experience serious, fatal side effects such as bleeding, heart problems, wounds that do not heal, and severe high blood pressure (27). In fact, the FDA has revoked the approval of Avastin for breast cancer patients because the efficacy is not worth the risks (28). If IsoFlow could be used to deliver Avastin, than treatment can be directly focused on the tumor and many normal cells involved in blood circulation can be avoided. In addition, the close-range delivery of Avastin to the tumor may increase the effectiveness of the drug. Avastin is just one of many drugs that can possibly be improved by catheters like IsoFlow. IsoFlow may benefit anticancer drugs that did not receive FDA approval because of poor safety. If these drugs could be used with IsoFlow, than their safety may be improved and the FDA may reconsider approval, bringing more anticancer drugs to market and saving or prolonging numerous lives. Not only may balloon catheters join radiation seeds as possible replacements for conventional radiation therapy, but the ability to deliver drugs as well may make them the universal medical device for cancer treatment. The promising future of devices like IsoFlow to minimize adverse effects and

improve safety highlights the importance of other medical devices that can deliver anticancer drugs, such as nanoparticles.

Nanoparticles

In the medical field, nanoparticles are spherical medical devices, usually between 1-100 nanometers, that can be inserted into the body of a patient to provide a therapeutic effect (29). Nanoparticles can be constructed out of several types of materials, but are usually made of lipids or biodegradebale polymers (29). Lipids are naturally occurring molecules that are present in cell membranes and polymers are large repeated molecules, such as cellulose, that can be either natural or synthetic (30). In cancer treatment, nanoparticles usually contain a therapeutic anticancer compound within the sphere, such as a small molecule drug. The main purpose of nanoparticles is to deliver the drug that it is carrying specifically to tumors and more efficiently than if the drug was administered alone. Nanoparticles are spontaneously more inclined to target tumors because of the enhanced permeability and retention effect (EPR effect). The EPR effect is a characteristic of tumor cells that is caused by angiogenesis. When tumor cells undergo angiogenesis, the new blood vessels are commonly leaky, and wider than preexisting, normal blood vessels. This makes the blood vessels of the tumor more prone to absorbing macromolecules, such as nanoparticles (31). If desired, the nanoparticles can be modified to further increase the chances of tumor cells being targeted rather than normal cells. This can be implemented several ways, such as by linking the exterior of the nanoparticle with tumor-specific compounds, or by linking the nanoparticle with photactivation properties so that the drug can only be activated in the presence of light. Nanoparticles release their anticancer agent into tumor cells when they make contact and spontaneously fuse with the tumor cell membrane (8). Although there are not any nanoparticle cancer treatments

available in the U.S. today, several preclinical trials are currently showing exceptional results, warranting their potential advantage in cancer treatment and fostering the initiation of human clinical trials.

Preclinical trials have been illustrating how nanoparticles can significantly decrease the incidence of adverse effects associated with standard chemotherapy. One preclinical trial showed how polymer nanoparticles loaded with the anticancer drug paclitaxel prevented lung tumor growth in over 70% of mouse models, without causing any toxicity (32). These results demonstrate how nanoparticles can decrease side effects by improving drug delivery because paclitaxel alone is known to cause hair loss, skin irritation, weight loss, and other toxicities in mice. The paclitaxel-loaded nanoparticles did not possess any tumor-specific properties, but local tumor delivery and the EPR effect were enough to eliminate chemotherapy side effects (32). Various research has also been conducted to test nanoparticles loaded with photosensitizers. Photosensitizers are compounds that cause cell death, after they are activated by light, by triggering Reactive Oxygen Species (ROS) formation (33). ROS are free radical products of oxygen metabolism, which occurs in every cell. High levels of ROS result in DNA damage, cell aging, and ultimately apoptosis in severe cases (34). After photosensitizers have been inserted into a patient, light is only exposed at the area of the tumor. Therefore, regardless of where photosensitizers are distributed throughout the body, only ones near the tumor should be activated. This should spare many normal cells from being harmed by the ROS damage. However, photosensitizers still cause side effects because of poor tumor specificity and are thus limited as a cancer treatment option. Some side effects of photosensitizers include skin burns and irritation, swelling, pain, and scarring (33). In one

preclinical trial, researchers attempted to specifically target tumor cells by placing photosensitizers into lipid nanoparticles and counting on the EPR effect. Results of the preclinical trial proved that the nanoparticles greatly decreased the side effects of photosensitizers in mouse models. Mice that received the photosensitizers alone experienced severe skin and liver damage four days after light activation, while mice that received the photosensitizers within nanoparticles were unharmed (35). In addition, since fewer photosensitizers were acting on normal cells and more were available to combat cancer cells, the tumors were eliminated more effectively than the photosensitizers alone (35). Therefore, by combining specific light exposure with a nanoparticle, photosensitizer side effects can be significantly diminished. The various successes of nanoparticles in preclinical trials have led to several candidates entering human clinical trials. For example, the nanoparticle Myocet has just begun Phase III trials in the United States for the treatment of breast cancer, and the nanoparticles SGT-53 (SynerGene Therapeutics-53) and INGN-401 (Introgen Therapeutics-401) are just starting Phase I trials for the treatment of lung cancer and solid tumors, respectively (36). Studies have demonstrated that the specificity of nanoparticles can decrease the side effects of small molecules; however, if there was a way nanoparticles could also improve the specificity of larger molecules, such as antibodies, than a truly effective approach to cancer treatment may arise.

Similar to photosensitizers, photoactivated compounds have been studied for use within nanoparticles. Researchers have hypothesized constructing nanoparticles that can start producing proteins within the body after photoactivation (37). These nanoparticles are made of lipids and contain all the machinery required for protein synthesis (amino

acids, DNA, ribosomes, etc.) inside the sphere. However, the DNA within the nanoparticle is bound to a photo-labile group, called DMNPE, (4,5-dimethoxy-2-nitrophenyl diazoethane) that prevents protein production until photoactivation (37). Just like with photosensitizers, light will only be exposed in the desired region of the body. This methodology was proven in mice when Green Fluorescent Protein was produced after light activation (37). This approach can be extremely advantageous in directly delivering large molecules that either cannot fit into particular nanoparticles in their final state or are usually quickly broken down by the body. For example, antibodies are large molecules that have made an incremental impact on cancer treatment, but some are plagued by serious side effects. Herceptin is an antibody used to treat breast cancer. Herceptin binds to the cellular receptor Her2, which is overexpressed in many breast cancers, and inhibits its activity (38). However, one of the most severe and troubling side effects of Herceptin is heart damage. This is caused because heart cells also possess the Her2 receptor. Therefore, Herceptin is probably binding to heart cells and inhibiting their normal function (39). If Herceptin can specifically target the Her2 receptors of breast tumor cells, the incidence of heart damage can be decreased. This specificity can possibly be obtained by incorporating the machinery required to produce Herceptin (with the DNA bound to a photo-labile group) within a nanoparticle. Once introduced into the patient, light will only be exposed to the areas of the breast that possess tumor cells. As a result, Herceptin should only be produced in these regions and heart cells should not be affected. This approach can possibly be used with other antibodies as well, such as Avastin, and illustrates the vast implications nanoparticles can have on the future of cancer treatment by providing specific delivery to various therapeutic agents.

Carbon Nanotubes

Similar to nanoparticles, carbon nanotubes (CNTs) are able to carry anticancer agents to tumors; however, they possess additional properties that make them unique medical devices. CNTs are biodegradable, hollow tubes made of carbon that have a diameter of about .4 to 100 nanometers (40). Anticancer agents can either be loaded within the CNTs or linked to the outside of the tubes. Once inserted into the body, CNTs enter cells by either passive diffusion or endocytosis, cellular uptake (40). Similar to nanoparticles, CNTs favor tumor cells because of the EPR effect, and tumor-specific compounds can be linked to the outside of the CNTs to guide them directly to tumor cells (40). Once inside the cell, there are several ways the drug can be released from the CNTs. If the therapeutic agent was linked to the outside of the CNTs, a linker would be used that is cleaved within the cytoplasm. Therefore, as soon as the CNTs enter a cell, the linker would be cut and the drug will be released (40). If the drug was loaded within the CNTs, the open ends would be sealed with molecules that can also be cleaved once they enter the cytoplasm (40). A concern that has hindered the success of CNTs, and nanoparticles, in clinical trials is that they can be harmful to any normal cells they enter (40). As a result, researchers have focused strongly on providing these devices with tumor-specificity as previously mentioned. Another advantage of CNTs is that their chemical structure allows them to act as heat conductors for thermal ablation (40). Thermal ablation is a method to eliminate tumors by inserting heat-generating materials into the cancer cells. Once a cell is heated above 55°C, the cell dies because of protein denaturation (40). Studies have shown that CNTs within cells can be heated by exposing

them to radiofrequency or near infrared wavelengths (40). These wavelengths would only be exposed in areas that possess tumor cells. Therefore, predominately tumor cells, and hardly any normal cells, will be destroyed because only tumor cells should both contain the CNTs and be exposed to the wavelength (40). CNT technology for cancer treatment is fairly new, so the majority of CNT optimism has been generated from animal studies and preclinical trials.

Studies have shown how CNTs can improve tumor-specificity of various anticancer drugs. Similar to nanoparticles, CNTs were used with the drug paclitaxel to see if side effects would be diminished. Results showed that CNTs linked with paclitaxel on the exterior of the tube did not cause any side effects in mouse models, and that tumor cells were eliminated more efficiently than paclitaxel alone (70% of tumor cells eliminated vs. 3%) (9). Several other studies showed that linking CNTs with folic acid derivatives greatly increased tumor-specificity of the anticancer drugs they were carrying (41). This approach was successful because tumor cells are known to overexpress folic acid receptors (41). Considering the link between tumor-specificity and diminished side effects, these findings are highly influential. Other studies have shown the advantage CNTs have in thermal ablation therapy. Without the use of CNTs, thermal ablation has been an ineffective treatment. Usually heat-conducting electrodes are inserted into tumors and exposed to radiofrequency or near infrared wavelengths. However, the electrodes deliver heat to many healthy cells surrounding and distant from the tumor cells. This causes side effects such as nausea, vomiting, fatigue, hair loss, skin irritation, acid reflux, and lack of salivary function (9). On the other hand, results of trials using CNTs showed complete elimination of tumor cells in rabbits after being exposed to radiofrequency

without any adverse effects (42). This highlights how CNTs can diminish side effects by improving treatment delivery. CNTs were able to seclude the delivery of lethal thermal energy to tumor cells, keeping normal cells healthy. The various findings illustrate that CNTs possess the same drug-carrying capabilities as nanoparticles with additional treatment benefits such as thermal ablation. If CNTs can combine chemotherapy and thermal ablation into a single treatment, than a convenient, powerful approach to attacking tumors would be generated.

Individually, chemotherapy and thermal ablation have limitations in certain instances. For example, one problem with chemotherapy is the occurrence of resistance. In some cases, such as the anticancer drug doxorubicin, a previously effective treatment does not work as well because some of the tumor cells develop resistances against the drug (43). This forces patients to undergo additional treatments to eliminate the remaining cancer cells, causing patients to experience more side effects. If one is concerned about resistance, than thermal ablation may be the appropriate treatment option; however, a limitation of thermal ablation is that it cannot be used if the tumor is larger than 5 cm (44). CNTs may be the answer to treating resistant tumors that are larger than 5 cm by simultaneously using chemotherapy and thermal ablation. The CNTs can be loaded with the anticancer drug and injected into the patient. Once the oncologist believes the drug has been delivered into the tumor cells and has completed its therapeutic effect, a radiofrequency or near infrared wavelength can be exposed at the tumor site to eliminate any tumor cells that were resistant to the anticancer drug. Therefore, chemotherapy can overcome the size limitations of thermal ablation and thermal ablation can remove the resistant cells that survived chemotherapy. Furthermore, this approach

can fight cancer more effectively by eliminating more tumor cells and avoids the side effects of the further treatments needed to treat the resistant cells. The unique properties of CNTs make them a versatile medical device that can diminish cancer patient side effects through several methods.

Microelectromechanical Systems

Other medical devices whose unique properties allow them to have substantial implications on cancer treatment are microelectromechanical systems (MEMS). MEMS are medical devices that basically act as small machines (about .02 to 1 millimeter) (10). In cancer treatment, a MEMS device would be implanted into the patient near the tumor site. The MEMS device would possess a reservoir that contains the desired drug, and a rechargeable battery (10). A tube would connect the drug reservoir to a region highly proximal to the tumor. The amount, rate, and time of drug release and battery recharging would be wirelessly controlled by an oncologist during each treatment visit (10). Once treatment is completely finished, the MEMS device can be safely removed by surgery (10). Another advantage of MEMS devices is that one device can contain several different drugs, each within a different reservoir. The release of each drug would be individually controlled by the oncologist (45). Co-administration of multiple drugs is a common theme in cancer treatment when a single drug is ineffective on its own (46). Although there are not any MEMS devices that have been tested in human patients today for delivering anticancer compounds, several have been constructed and implanted into animal models (45, 47).

One animal study demonstrated how a MEMS device could improve the drug delivery of an anticancer drug used to combat brain tumors. Brain cancers are usually difficult to treat because of the blood-brain-barrier. Since anticancer drugs are mostly orally delivered, they must bypass the blood-brain-barrier to reach the brain tumor cells.

However, the blood-brain-barrier is difficult to penetrate and even some of the best brain cancer drugs have difficulty getting to the brain. As a result, more drug molecules are available to harm normal cells outside the brain (47). For example, temozolomide is a brain cancer drug whose affect on normal cells causes side effects such as difficulty walking or coordinating movement, confusion, anxiety, seizures, infection, urinary incontinence, and several others (48). Researchers designed a MEMS device that can be implanted within the skull and locally deliver temozolomide to brain tumor cells. Results showed that the most efficient MEMS device significantly increased the survival of rats with brain cancer (47). About 43% of the rats survived for the entire study period (120 days) and the median survival was 40 days (47). Implanting the MEMS within the skull increased treatment efficiency because the blood-brain-barrier was avoided and more temozolomide was able to directly act on brain tumor cells. In addition, the side effects that are caused by temozolomide being outside of the brain would theoretically be avoided. Another study utilized a MEMS device to exploit the advantages of siRNA (49). SiRNA (small interfering RNA) is an RNA molecule that can silence the expression of a gene with the complementary nucleotide sequence (50). One of the limitations of siRNA is that they can be easily degraded in the body by enzymes (50). An encasing structure, such as a MEMS device, is required to protect the siRNA from enzymatic degradation so that it can be safely delivered to tumors. In this study, a MEMS device was able to directly deliver siRNA that silences the gene expressing SPK-1, a radioresistant protein found in tumor cells (49). Radioresistant proteins help tumor cells survive radiation, pressuring oncologists to administer higher doses. However, there is a limit to the amount of radiation exposure a patient can receive in a lifetime before it becomes severely

damaging or fatal (51). Therefore, being able to use lower doses of radiation has always been desired so that fewer normal cells are damaged and the maximum capacity of radiation exposure is less likely to be reached. The researchers intended on using the siRNA to make the tumor cells more sensitive to radiation therapy. Testing the device in mice demonstrated that tumors regressed over 50% after MEMS siRNA delivery and radiation therapy (49). Therefore, the increased vulnerability of tumor cells means a lower dosage of radiation can potentially be used, decreasing the amount of normal cells harmed. The MEMS device improved the delivery of siRNA so that the side effects of radiation therapy could be diminished. As technology improves and MEMS devices become optimized, the number of cancers that can possibly be treated and drugs that can be delivered should amplify.

A limitation of MEMS devices is that the requirement of a battery increases the size of the device. In some cases, the large size of the MEMS device prevents it from being used to treat some cancers because of unsuitable implantation areas. However, one study demonstrated the success of a battery-less MEMS device (52). Rather than using a battery, the drug is released after applying a magnetic field, which removes a magnetic seal that is blocking the drug. Results showed that the device successfully delivered the anti-proliferative drug docetaxel (52). Although this study was mainly intended for treating proliferative retinopathy, one can understand the potential of this device for treating proliferative cells in cancer. Perhaps other methods can be considered for activating drug releases, such as light activation, similar to releasing drugs in nanoparticles. Since a battery-less MEMS device would possibly increase the amount of cancers that can be treated, more patients would be able to avoid the side effects of taking

their anticancer drug alone. However, a limitation that has deterred the clinical progress of MEMS devices is that they can be damaged by moisture or external conditions within the body of a patient (10). The methods required to protect the device usually limit its functionality (10). Therefore, device design must be optimized so that the MEMS device is simultaneously protected and effective. The quick advancement of modern technology supports the hope that MEMS devices will be clinically successful. Similar to the previous medical devices discussed, MEMS devices can diminish the side effects of future cancer treatments by focusing delivery mainly on tumor cells and evading normal cells.

Conclusion

Medical devices can perform a wide variety of functions that can be used in the medical field. One of the many areas where medical devices can provide assistance is in treatment delivery. This is especially important in cancer treatment because poor treatment delivery is known to result in adverse effects in patients. These adverse effects not only endanger the well-being of a patient, but also hinder the application of potential or existing cancer treatments. Side effects are mainly a result of the treatment not being specific or directed towards tumor cells. Medical devices such as radiation seeds and balloon catheters have shown to deliver radiation without causing many of the side effects associated with conventional radiation therapy. Loadable medical devices such as nanoparticles, carbon nanotubes, and MEMS devices have demonstrated that specifically and/or locally carrying drugs to tumor sites significantly diminishes side effects compared to using the drug alone. By enhancing safety, this can improve existing drugs, increasing treatment options for cancer patients, and can magnify the probability of FDA approval of future drugs. The construction of these devices fosters interest in the capabilities of future devices that are intended to improve treatment delivery. One can imagine that the nano-sized robots that are commonly discussed in movies would be the ideal medical devices for treatment delivery. Researchers have hypothesized that these nanobots, or pharmacytes, can possibly be constructed (53). The pharmacytes would be mini robots that are about the same size as nanoparticles, but would be self-powered and wirelessly controlled like MEMS devices. The pharmacytes would be able to carry therapeutic agents directly to tumors, without ever harming normal cells (53).

Understanding that these characteristics of size, wireless control, and drug carrying ability have already been obtained in current medical devices, pharmacytes may actually become a reality. Nevertheless, the various examples and results illustrate how medical devices can diminish or eliminate the side effects of cancer treatment by improving treatment delivery.

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