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IMPLANTS FOR DIFFERENT TYPES OF CANCER: AN UPDATED REVIEW

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Abstract

Cancer, a significant global health concern, accounts for one in six deaths worldwide. The complex landscape of cancer treatment includes conventional approaches such as surgery, chemotherapy, and radiotherapy, as well as recent advances like stem cell therapy, targeted therapy, ablation therapy, and various nanomedicines. Notably, electrospinning has incorporated colloidal nanoparticles into polymeric NFs for drug delivery and cancer treatments. The unique contribution of this review lies in its focus on recent investigations that aim to enhance drug delivery and improve the efficiency of cancer treatments. Biomaterials have been applied to immunotherapies to modulate immune cells and the immunosuppressive tumor microenvironment, aiming to enhance both efficacy and safety. Stem cell therapy shows promise in regenerating tissues affected by cancer, while targeted therapy specifically inhibits the growth of cancer cells with minimal damage to healthy cells. This review provides an updated overview of implant applications in cancer therapies.

Keywords: Electrospun Nanofibers; Cancer Treatment; Drug Release; Nano Medicine; Biocompatible Polymers; Hyperthermia.

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Introduction

Cancer is a complex series of disease states marked by a gradual loss of control over growth. For many decades, patients had limited treatment options, predominantly relying on single or combined approaches such as surgery, radiation therapy, and chemotherapy [1].

In contrast to conventional systemic administration, implantable drug delivery devices present numerous benefits. The strategic implantation allows for circumventing the absorption and distribution challenges associated with oral and peripheral approaches, leading to elevated drug concentrations at specific sites. Consequently, implantable drug delivery technologies enhance site-specificity and tackle medication non-adherence, bringing about a transformative impact on the clinical management of

chronic diseases [2].

Moreover, the promotion of tumor growth and the establishment of metastatic implants through angiogenesis are impacted by the increased expression of specific proteases, such as MMPs [3]. There are five primary categories of immunotherapy: immune checkpoint blockade (ICB) therapy, cytokine therapy that promotes lymphocytes, chimeric antigen receptor T-cell (CAR-T) therapy, agonistic antibodies, and tumor vaccines. Among these, immune checkpoint blockade (ICB) therapy has been extensively investigated and studied as the most comprehensive class of immunotherapy to date [4]. Enhancing the effectiveness of chemotherapeutic treatments for cancer patients faces a significant challenge in the limited capacity to target tumor cells specifically, thereby minimizing toxicity to healthy cells. This difficulty results in an inability of antitumor molecules to boost their therapeutic response, leading to a bleak prognosis and severe health complications associated with prevalent pathologies. To overcome these limitations and enhance efficiency, innovative strategies are emerging [5, 6, 7].

Ongoing research has significantly broadened our understanding of safety concerns related to silicone

breast implants since the FDA-imposed moratorium in the 1990s. Plastic surgeons have a responsibility to prioritize patient care by fostering accountability within the industry and among their peers [8].

Recent research has proposed extracellular vesicles (EVs) as a novel mechanism facilitating cellular communication within or between tissues. Additionally, numerous studies have highlighted the potential use of EVs in both diagnosis and treatment [9].

As life expectancy rises, the prevalence of these diseases is on the ascent, posing a challenge for ophthalmologists given their substantial impact on the quality of life for affected individuals. [10]

Non-Hodgkin's lymphoma (NHL), the most prevalent hematological malignancy globally, encompasses a diverse spectrum of B-cell and T-cell proliferations [11].

Trophoblasts represent the initial cells embarking on a sophisticated differentiation program. Mononucleated cytotrophoblasts (CTBs) possessing stem cell-like characteristics undergo spontaneous fusion, giving rise to multinucleated syncytiotrophoblasts [12].

Biomaterials have evolved into potent tools for drug delivery and targeted localization, enabling precise management of loaded agents in terms of both space and time [13].

Implants are artificial devices designed for insertion into the body to replace or support a biological structure, offering functionalities such as drug delivery and monitoring body functions [14].

Implantable Sensors for Early Cancer Detection:[21,22]

> Timely Detection through Implantable Sensors:

Explore the pivotal role played by implantable sensors in the early diagnosis of cancer by effectively identifying crucial biomarkers associated with various cancer types. This innovative approach significantly contributes to the potential for early intervention, ultimately improving patient outcomes.

Uninterrupted Surveillance with Implantable Sensors:

Illuminate the advancements in research that showcase how implantable sensors serve as an instrumental tool for continuous monitoring of dynamic physiological changes. These sensors, seamlessly integrated within the body, offer an uninterrupted stream of real-time data, providing clinicians with invaluable insights into the progression and fluctuations in the patient's health status.

Nano fibers for Drug Delivery

The passage delves into the application of nanofibers (NFs) in drug delivery, particularly emphasizing the encapsulation of diverse drugs through

electrospinning methods. The process of coaxial electrospinning is highlighted, illustrating its use in creating core/shell NFs, exemplified by the combination of paclitaxel (PTX) and polymer. The exploration extends to incorporating low-water soluble molecules, hydrophilic antibiotics, and chemotherapeutic agents like doxorubicin and cisplatin, underscoring their efficacy in antimicrobial and chemotherapy contexts. Furthermore, NFs are scrutinized for their potential in mitigating side effects, as evidenced by the development of mucoadhesive nano-carrier DOC-PVA for oral cancer treatment. Lastly, the integration of Lovastatin, a cholesterol-lowering drug, into biocompatible NFs is discussed as an approach for drug delivery [7].

> Stimuli-Responsive Nanofibers

As mentioned earlier, synthetic polymers have been extensively utilized as matrices in the creation of nanofibers (NFs) for drug delivery investigations. However, recent efforts in research have focused on exploring stimuli-responsive systems [15]. These systems can undergo changes triggered by external factors like temperature, pH, ion strength, or solvent properties [16-18].

> Thermo-Responsive Nanofibers

The passage provides an overview of diverse strategies for developing temperature-sensitive nanoformulations with potential applications in biomedicine, specifically in drug delivery for cancer treatment.

Nanoformulations for Dual-release:These formulations respond to both temperature and pH stimuli, exemplified by poly(N-isopropylacrylamide-co-acrylic acid) NFs in thermoplastic polyurethane (TPU).

Electrospun Self-immolative Polymer (SIP)/PAN Fibers: Explored for the rapid release of transported molecules in response to an external stimulus. The passage also covers the integration of carbon nanotubes, magnetic nanoparticles, and gold nanoparticles into electrospun nanofibers, enhancing mechanical and drug delivery properties. These hybrid structures show promise in cancer therapy, including hyperthermia treatments and combination therapies. The potential toxicity of certain nanoparticles is addressed, emphasizing the importance of surface functionalization to mitigate adverse effects [7, 2].

Biomedical implants

Bioactive implants have the capability to induce changes in the adjacent tissue through their inherent biomaterials, drug release mechanisms that trigger bioactivity, or the inclusion of cells capable of generating bioactive molecules. The ensuing sections delve into the bioactivity induced by drugs and cells within implants, encompassing their roles in drug delivery and tissue regeneration [14].

Bioactive implants can integrate therapeutic agents like small chemicals, peptides, proteins, hormones, or cells with the intent of providing therapeutic benefits within the human body. These drug delivery systems are typically administered through parenteral routes, such as injection or implantation [14].

Implantable Patches: Pioneering Cancer Therapeutics [23, 24, 25]

In the ever-evolving realm of cancer therapeutics, implantable patches have emerged as a groundbreaking tool, presenting a sophisticated approach to the targeted and continual delivery of therapeutic substances. Crafted from biocompatible materials, these patches signify a propitious pathway for precision medicine in cancer treatment.

Precision Delivery and Targeting

Implantable patches offer an innovative solution to the intricacies of drug delivery, ensuring the direct administration of therapeutic agents to the precise tumor site. This targeted strategy mitigates systemic exposure, potentially diminishing side effects and amplifying the overall effectiveness of cancer treatments.

Sustained Release for Prolonged Effect

A primary advantage of implantable patches is their capacity to facilitate the protracted release of therapeutic compounds. This sustained exposure holds the potential to augment the therapeutic impact on cancer cells, providing a more encompassing and enduring treatment effect.

> Overcoming Biological Barriers

Demonstrating significant potential, implantable patches have exhibited effectiveness in surmounting biological barriers that traditionally impede the success of conventional drug delivery methods. Through the controlled release of therapeutic agents, these patches may elevate drug penetration into tumors, addressing challenges linked to drug resistance.

Advantages [23, 24]

Implantable patches in the field of cancer therapeutics present a multitude of advantages that underscore their increasing importance in medical research. These benefits encompass:

1. Precision Targeting

Implantable patches facilitate the precise delivery of therapeutic agents directly to the tumor site, thereby diminishing systemic exposure and mitigating offtarget effects.

2. Sustained Release

The capacity of implantable patches to provide prolonged release of therapeutic compounds ensures a sustained and consistent impact on cancer cells, potentially amplifying the efficacy of treatment.

3. Minimized Side Effects

By delivering drugs directly to the tumor, implantable patches have the potential to curtail

systemic side effects associated with traditional chemotherapy, thereby enhancing the overall safety profile of cancer treatments.

4. Overcoming Drug Resistance

Implantable patches have the potential to surmount biological barriers and drug resistance by delivering therapeutic agents in a controlled and targeted manner, enhancing drug penetration into tumors.

5. Enhanced Patient Compliance

The controlled and continuous release of drugs from implantable patches may enhance patient compliance by eliminating the need for frequent dosing.

6. Personalized Medicine

The precision afforded by implantable patches aligns with the tenets of personalized medicine, enabling tailored treatment approaches based on individual patient profiles.

7. Reduced Treatment Frequency

Implantable patches, with their sustained release capabilities, hold promise in reducing the frequency of treatment administrations, providing convenience and potentially elevating the quality of life for patients [2].

As the field progresses, ongoing research and clinical investigations continue to validate and refine these advantages.

For Prostate Cancer

Vantas® and SUPPRELIN® LA 50 mg, which are histrelin acetate implants, are employed in the context of prostate cancer. Viadur® from Bayer Healthcare Pharmaceuticals in Berlin, Germany, stands out as a non-biodegradable titanium osmotic implant. This implant employs a DUROS® controlled release pump to dispense leuprolide acetate, an analog of gonadotropin-releasing hormone, for a period of 12 months. This administration is intended for the palliative treatment of advanced prostate cancer [2]. Information pertaining to alginate implants for the treatment of pancreatic tumors indicates some compromise in pancreatic activity when compared to untreated controls without a scaffold [13].

Implantable patches hold promise in overcoming biological barriers inherent in prostate cancer treatment. By providing controlled release, these patches may enhance drug penetration into prostate tumors and address challenges associated with drug resistance [38].

For Ovarian Cancer

Ovarian cancer (OvCa) stands as the most fatal among gynecological cancers, with a mere 48.8% overall survival rate over a five-year period [19]. This diminished survival likelihood is attributed to the absence of noticeable clinical symptoms during the initial phases of metastasis. The formation of a metastatic tumor involves the dynamic interplay between malignant cancer cells and the tumor

microenvironment. In ovarian cancer, the tumor microenvironment has the capacity to enhance the expression of proteases, influencing crucial aspects such as adhesion, motility, matrix remodeling, and angiogenesis.[3] Implantable patches offer a sophisticated solution for precision drug delivery in ovarian cancer. Through localized administration, therapeutic agents are directed specifically to the ovarian tumor site, minimizing systemic exposure and mitigating potential side effects [36].

For Bladder Cancer

Clinical trials are presently underway for intravesical osmotic pumps. GemRIS™ successfully concluded a phase 1b clinical trial, evaluating its safety and tolerability in patients with muscle-invasive bladder cancer. Furthermore, GemRIS™ is scheduled for additional phase 1b clinical trials, including one with Opdivo® (nivolumab) in the same patient population, along with two other trials focusing on non-muscle-invasive bladder cancer and muscle-invasive bladder cancer in individuals unfit for radical cystectomy [2].

Paraneoplastic Visual Syndromes

Paraneoplastic visual syndromes encompass a diverse array of conditions linked to a systemic malignancy that lacks a direct connection to ocular factors.[10]

Melanoma-Associated Retinopathy: MAR represents a rare autoimmune disorder associated with cutaneous melanoma, presenting as a paraneoplastic syndrome. It leads to progressive visual field loss and night blindness in affected individuals. In a study by Karatsai et al., a 73-year-old woman, monitored for three years post-FAc implantation in both eves. exhibited significant improvement in visual symptoms, visual field, and best-corrected visual acuity (BCVA) from 20/80 to 20/20 shortly after the implant. The BCVA remained stable at 20/20 throughout the three-year follow-up. Retinal function, assessed electroretinography (ERG), showed improvement in the right eye one year postimplant and in the left eye after two years [10].

For Cancer Immunotherapy

A range of biomaterials, encompassing nanoparticles, implantable biomaterial scaffolds, and injectable biomaterial scaffolds, have been introduced to stimulate immune responses and enhance the efficacy of anti-tumor interventions. Scientists have devised implantable biomaterial scaffolds capable of carrying immune agents, bioactive factors, or cells to combat tumors. These scaffolds, synthesized from polymerized alginate, are designed to address locally advanced or unresectable tumors by recruiting and activating immune cells [4].

The sustained release of immunotherapeutic agents

from implantable patches contributes to prolonged immune cell activation. This prolonged exposure can lead to heightened and sustained anti-tumor immune responses, potentially improving the overall effectiveness of cancer immunotherapy [28].

For Breast Cancer

The extensive research on breast cancer incidence in individuals with silicone implants consistently indicates no link between these implants and breast cancer. Following the Institute of Medicine's suggestion that breast implants might affect routine mammographic screening accuracy, several case reports speculated that opaque breast implants could impede mammographic breast visualization and physical breast examination. This, in turn, could lead to delayed breast cancer diagnosis and poorer prognosis. However, these reports had significant flaws, as many included women who underwent screening mammography without employing the Eklund implant displacement technique [8].

The prevalent diagnosis was breast cancer, succeeded by colon cancer and gastric cancer. A considerable portion of patients presented with clinical stage III/IV disease upon diagnosis. Over 50% of the patients underwent a single round of chemotherapy, with the remaining individuals opting for multiple lines of treatment delivered through the same port-a-cath. Notably, two patients abstained from receiving any cytotoxic chemotherapy [20].

For Skin

A light-responsive, swiftly detachable microneedle (MN) patch designed to expediently transport drugloaded MNs to the skin, enabling recurrent administration of chemotherapy and photothermal therapy to superficial tumors through light activation. The MNs, composed of a PCL polymer containing photosensitive nanomaterials LaB6 (lanthanum hexaboride) serving as photothermal transducers and the anticancer drug doxorubicin (DOX), were employed for cancer treatment. [20]

Techniques [14]

• Three-Dimensional Printing (3D Printing)

Three-dimensional (3D) additive printing, an manufacturing (AM) technique pioneered at the Massachusetts Institute of Technology in the 1990s, involves converting Computer-Aided Design (CAD) into a Stereo Lithography (STL) file. This STL file is then utilized by the 3D printer to manage material movement and deposition. Copper/tetrakis(4-carboxyphenyl) porphyrin/β tricalcium phosphate (Cu-TCPP-TCP) is the employed material, with applications in bone tumor ablation and osteogenesis. The resulting outcome is metalorganic photothermal nanosheets, demonstrating the promotion of osteosarcoma cell death in vitro, ablation of subcutaneous bone tumor tissue in vivo, adhesion of bone marrow MSCs and HUVEC in vitro, MSCs differentiation into osteocytes, HUVEC expression of angiogenesis markers in vitro, and enhanced bone regeneration in vivo.

• E-Jet 3D Printing

E-Jet 3D printing involves the use of Poly(lactic-co-glycolic acid) and drugs (5-fluorouracil and NVP-BEZ235). The primary application is drug delivery in orthotopic breast cancer, resulting in long-term drug release near the tumor site.[14]

Disadvantages

- Risk of infection: Implants, whether for drug delivery or other purposes, may pose a risk of infection at the implantation site, which can compromise patient health.[32]
- Biocompatibility issues: Some patients may experience adverse reactions or rejection of the implant due to issues with biocompatibility, leading to inflammation or other immune responses[33]
- ➤ Invasive Procedure: Implantation of devices involves a surgical procedure, which carries inherent risks and may not be suitable for all patients, particularly those in poor health.[34]
- Complexity of removal: Some implants may be challenging to remove or adjust once they are in place, potentially limiting their adaptability to changing patient needs.[35]
- Limited drug payload: Implants may have limitations on the amount of drug they can carry, potentially restricting their efficacy, especially for long-term treatments.[38]

Applications

Implantable patches exhibit a wide array of applications across various medical domains, underscoring their adaptability and substantial impact. The ensuing applications delineate the manifold roles of implantable patches, substantiated by pertinent references:

Cancer Therapeutics [26]

Implantable patches assume a pivotal role in the realm of cancer treatment by facilitating targeted and sustained delivery of therapeutic agents directly to tumor sites. This strategic approach minimizes systemic exposure, thereby significantly improving treatment efficacy and mitigating potential side effects associated with conventional cancer therapies.

Neurological Disorders [27]

Implantable patches emerge as a beacon of hope in the treatment of neurological disorders. By providing a specialized platform for localized drug delivery to the brain, they address the formidable challenges posed by the blood-brain barrier. This innovation signifies a potential breakthrough in the therapeutic landscape for neurological conditions.

Cardiovascular Interventions [28]

In the field of cardiology, implantable patches are undergoing exploration as a groundbreaking

avenue for controlled drug release. Specifically, these patches hold promise in addressing post-myocardial infarction remodeling and fostering enhanced cardiac regeneration. The localized and sustained drug delivery mechanism offers a tailored approach to cardiovascular interventions.

Diabetes Management [29]

In the realm of diabetes care, ongoing investigations focus on the application of implantable patches for controlled insulin delivery. This avenue presents a potential paradigm shift, offering a more convenient and efficient alternative to traditional methods of insulin administration. The precise and controlled release of insulin enhances therapeutic outcomes for individuals managing diabetes.

Orthopedic Applications [30]

The exploration of implantable patches extends to orthopedic applications, where they play a role in facilitating localized drug delivery. This approach holds promise in enhancing bone regeneration and addressing conditions such as osteoarthritis. Implantable patches present a novel avenue for optimizing therapeutic outcomes in orthopedic treatments

Wound healing [31]

Implantable patches find application in the domain of wound care, where they serve as vehicles for the delivery of growth factors or antimicrobial agents. This targeted delivery system contributes to accelerated wound healing processes while minimizing the risks of infections. The use of implantable patches represents a significant advancement in wound management.

Conclusion

In conclusion, implantable patches mark the advent of a transformative era in cancer therapeutics, presenting a hopeful strategy to elevate precision and effectiveness in treatment. As advancements in this domain unfold, these patches have the potential to assume a central role in influencing the trajectory of personalized cancer care in the future. The investigation delves into the fusion of biomaterials with immunotherapy as a means to tackle complexities in cancer treatment, specifically within the intricate tumor microenvironment. Implantable and injectable biomaterial scaffolds emerge as a promising avenue for elevating drug delivery systems. Hurdles, including insufficient lymphocyte accumulation and dosage constraints stemming from autoimmunity in immunotherapies, are examined. Biomaterial-driven delivery approaches aspire to regulate lymphocytes, refine drug precision, surmount obstacles, and curtail side analysis effects. Additionally, the encompasses electrospinning methodologies for crafting polymeric nanofibers (NFs) applicable to drug delivery and cancer treatments. The emphasis lies on hybrid NFs and their pivotal role in amplifying drug delivery efficacy and

diminishing solid tumors through magnetic and plasmonic hyperthermia.

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Conflicts of Interests

There are no conflicts of interest.

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All the authors have contributed equally.

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