

Nanotechnology in Bladder Cancer

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Abstract: *Bladder cancer (BC) is the second most common cancer of the urinary tract in men and the fourth most common cancer in women, and its incidence rises with age. There are many conventional methods for diagnosis and treatment of BC. There are some current biomarkers and clinical tests for the diagnosis and treatment of BC. For example, radiotherapy combined with chemotherapy and surgical, but residual tumours cells mostly cause tumour recurrence. In addition, chemotherapy after transurethral resection causes high side effects, and lack of selectivity, and low sensitivity in sensing. Therefore, it is essential to improve new procedures for the diagnosis and treatment of BC. Nanotechnology has recently sparked an interest in a variety of areas, including medicine, chemistry, physics, and biology. Nanoparticles (NP) have been used in tumour therapies as appropriate tools for enhancing drug delivery efficacy and enabling therapeutic performance. It is noteworthy, nanomaterial could be reduced the limitation of conventional cancer diagnosis and treatments. Since, the major disadvantages of therapeutic drugs are their insolubility in an aqueous solvent, for instance, paclitaxel (PTX) is one of the important therapeutic agents utilized to treating BC, due to its ability to prevent cancer cell growth. However, its major problem is the poor solubility, which has confirmed to be a challenge when improving stable formulations for BC treatment. In our review we have discussed about the technology and diagnosis and treatment in bladder cancer.*

Keywords: bladder cancer, diagnosis, treatment, nanotechnology, chemotherapy

1. Introduction

One common malignancy that has a high fatality rate is bladder cancer (BC). Bladder cancer is expected to cause 83, 730 new cases and 17, 200 fatalities. In the United States, 2021 [1]. Based on the invasive depth, BC is divided into two groups: 25% of new cases are muscle invasive bladder cancer (MIBC), also referred to as metastatic malignancies, and 75% of new cases are non - muscle invasive bladder cancer (NMIBC). Urine cytology and cystoscopy are the gold standards for identifying breast cancer (BC); magnetic resonance imaging (MRI) has been suggested for stage evaluation. Transurethral resection of bladder tumours (TURBT) is the primary treatment method for non - malignant intra bladder (NMIBC). Intravesical injections of immunotherapy or chemotherapy are used as a post - TURBT strategy to try and stop the disease from progressing and coming back. The usual treatments for MIBC include radiation therapy and urinary diversion, either with or without adjuvant therapies. Conversely, a radical cystectomy produces serious side effects and reduces quality of life. In actual practice, other treatments that are often given include radiation, chemotherapy, TURBT, and thus a medication that spares the bladder. [3] - [4].

Targeted medications and immunotherapies have shown tremendous promise for the treatment of bladder cancer as our understanding of the biology of the disease has expanded [5]. For advanced MIBC, the FDA approved erofitinib, a kind of FGFR inhibitor, and Avelumab, an anti - PDL1 medication [6] - [7]. Many other targeted or immunotherapy medications are undergoing clinical studies [8].

All these therapeutic strategies do not improve the diagnostic or treatment plan for BC. Urine cytology and magnetic resonance imaging (MRI) are less sensitive in detecting or staging breast cancer [9]– [11], while cystoscopy is a painful, costly, and invasive treatment. The recorded rate of recurrence was Visual Synopsis Journal of Nanobiotechnology, 2021, 19: 393; Page 3 of 18 Xu et al., despite multiple measures to prevent the onset and progress. 50% to 90% in five years for NMIBC [12] - [13].

Thus, further techniques are badly needed to improve BC therapies' therapeutic and diagnostic efficacies. Nanotechnology has been documented in several studies as a unique approach to the treatment of breast cancer. Nanotechnology shows great promise for clinical application by mitigating the shortcomings of current medicinal approaches. Properly engineered nanoparticles can enhance the effectiveness of existing therapeutic methods or identify cancer biomarkers with acceptable specificity and accuracy. Additionally, NP - based delivery methods can enhance targeted localization to tumour locations and active cellular absorption, reducing side effects and minimizing harm to normal cells. Furthermore, in order to improve the antitumor efficaciousness, NPs are employed to extend the residence period of intravesical drugs [15] - [16].

Additionally, to increase effectiveness even further, nanotechnology can be combined with other cutting - edge technologies (such as phototherapy and radiotherapy). More accurate and dependable methods for the diagnosis and treatment of BC should emerge as nanotechnology and ontogenetic pathways are more understood and developed.

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Preclinical research on bladder cancer has made tremendous strides in the last few years. However, we believe that the field has advanced to the point where a review article such as ours will be interesting to a broad audience. Over the previous three years, a number of groups also examined the use of nanotechnology in urological or bladder malignancies [17]–[19].

Our review, however, concentrated on the various approaches to diagnosis and treatment and the possible applications of nanotechnology in these procedures which may be useful for future designing and investigating novel nano systems for BC management. The majority of their studies, however, were summarized based on the fundamental structure of nanoparticles. Since many different research were referenced in both our review articles and the others, we think all of these review articles are educational and can give readers a variety of viewpoints.

1.1 Bladder structure

The kidneys secrete urine, which is stored in the bladder, a hollow organ. The bladder has a lumen size of 400–600 mL. An urge to pee is triggered when the volume of urine reaches approximately 150–300 mL [20]. Because the bladder wall is elastic and impermeable, urine can be temporarily stored in the bladder while confined waste products and urine cannot pass through the wall. The wall of the bladder is made up of several tissue layers. Adventitia, detrusor muscle, submucosa, and mucosa, which is made up of lamina propria and transitional epithelium (urothelium), are the layers that go from outside to within. The bladder permeability barrier is provided by the urothelium, which is the first lining layer inside the bladder lumen [21]. The basal cells, intermediate cells, and umbrella cells (ordered from outside to inside) make up the urothelium [22]. The unique morphologies of these three cell types vary [23]. 20 µm - diameter intermediate cells are formed when basal cells, which have sizes of 5–10 µm, merge together.

1.2 Permeability barrier

Two notable physical characteristics that set umbrella cells apart from basal and intermediate cells are [22]. The asymmetric unit membrane is formed by the scalloped - shaped plaques that cover the apical membrane, making the outer leaflet thicker than the inner leaflet [24]. Second, cytoskeletal fibrils are linked to many cytoplasmic vesicles found in umbrella cells [25]. About 1000 subunits make up each plaque above the umbrella cell membrane, which is made up of four uroplakins: UPIII (47 kDa), UPIa (27 kDa), UPIb (28 kDa), and UPII (15 kDa) [26]. Every subunit is structured in a hexagonal pattern, with six large particles (UPIa or UPIb) making up the inner loop and six little particles (UPII or UPIII) making up the outside loop [20], [22], [27]. The tight arrangement of these scalloped - shaped plaques establishes the barrier function of umbrella cells, which is further strengthened by a mucin layer on the luminal side. GAGs (glycosaminoglycans), which are hydrophilic and create an aqueous coating atop umbrella cells, make up this mucin layer. Consequently, this GAG layer can stop urine materials from sticking to the bladder lumen [28].

1.3 Bladder cancer

More than 90% of bladder malignancies, or urothelial carcinomas, originate from bladder urothelial cells. Additional forms of bladder cancer include adenocarcinoma, which originates from the cells that make up glands, and squamous cell carcinoma, which starts from squamous cells as a result of persistent bladder inflammation. Bladder cancer occurrence is correlated with numerous factors. Firstly, the most powerful risk factor for bladder cancer is smoking [29] - [30]. Bladder cancer has been linked to specific compounds found in cigarettes [31]. Bladder cancer is also influenced by occupational exposure to some carcinogens including aromatic amines and benzidine. Bus drivers, rumblers, motor mechanics, leather workers, blacksmiths, machine setters, and mechanics are among the professions with a high risk of bladder cancer [32]. Third, as salted and grilled meats include carcinogens such as N - nitroso compounds and heterocyclic amines, they may also be linked to bladder cancer [33]. A positive cytology result is followed by a cystoscopy and biopsy to confirm the diagnosis of bladder cancer. Urinary frequency, urgency, dysuria, painless gross hematuria (the presence of red blood cells in the urine), and bladder irritation are common signs of bladder cancer. Tumor location and spread determine the stage of bladder cancer.

1.4 Painful bladder syndrome

(PBS) Painful bladder syndrome (PBS), commonly referred to as interstitial cystitis, is a chronic bladder pain illness that excludes other abnormal bladder disorders and is characterized by symptoms of irritation, nocturia, urgency, and frequency [34]– [37]. PBS is a persistent, disabling illness that negatively affects sufferers' quality of life [38]. Bladder cancer or endometriosis are two examples of urological disorders that can cause PBS [39]– [44]. All suggested treatment strategies are grounded in empirical data because the etiology of PBS is still not fully known [38].

Infection, allergic reaction, autoimmune response, neurogenic inflammation, urothelial dysfunction, and hereditary variables are among the reasons that cause PBS [45] - [46]. Numerous investigations have suggested that bladder irritation is the cause of PBS symptoms [47]. Additional research using PBS on animals demonstrated that the build - up of neutrophils in the bladder wall results in a high level of inflammatory cytokines and also triggers some expression of inflammatory genes [48] - [49].

1.5 Bladder cancer treatment and nanotechnology:

Delivery of intravesical medications Because the medications are only applied locally, intravesical instillation therapy for BC offers several benefits, such as a high local drug concentration and little systemic toxicity. The most often utilized medications are chemotherapeutic agents and Bacillus Calmette - Guerin (BCG). However, the drug's effectiveness was severely hampered by systemic and local adverse effects, urine dilution, inadequate bladder wall penetration, and unstable agents in low urine pH.

1.6 BCG loaded nanoparticles

An adjuvant postoperative treatment for NMIBC is live BCG instillation intravenously, particularly for high - grade tumors and carcinoma in situ. But there is still a risk of side effects, like severe urinary symptoms, systemic infections, and sepsis, which could force the suspension of BCG therapy [50]. The active immunoadjuvant component of BCG, known as the BCG cell wall skeleton (BCG - CWS), can be utilized in place of live BCG [51]. However, because BCG - CWS is poorly soluble and has a low absorption by cancer cells, its use in clinical settings is limited. Using the emulsified lipid (LEEL) approach, liposomes loaded with BCG - CWS (CWS - NP) were created in order to get around this problem. In both human and rat model cells, the CWS - NP/LEEL system was shown to have anticancer effects without causing any discernible side effects. Furthermore, in the T1/T2 balance, the CWS - NP/LEEL may decrease T2 cells and increase T1 immunity [52]. Additionally, cationic chitosan nanoparticles as a BCG delivery method were assessed. The positive surface charge, high tumor targeting, and nano range size of BCG loaded cationic NPs allowed them to overcome the bladder permeability barrier and exhibit strong anticancer efficacies, resulting in an enhanced delivery rate [53].

1.7 SPIONs and SeD loaded nanoparticles

SeD - loaded nanoparticles and SPIONs It has been shown that local hypoxia is a crucial component of the tumor microenvironment and has a major role in treatment resistance [54] - [55]. In order to release the hypoxia in bladder cancer through intravesical instillation, Weiqiang et al. produced superparamagnetic iron oxide nanoparticles (SPIONs) loaded nanoscale oxygen generator (PLZ4[at]SeD) with bladder cancer targeting moiety [56]. The MRI contrast efficiency was improved by the nanoparticles' excellent tumor permeability and targeting ability to three bladder cancers taken from patients.

1.8 Deguelin loaded nanoparticles

To distribute deguelin (D/DMP), cationic DOTAP and monomethoxy poly (ethylene glycol) - poly (ϵ - caprolactone) hybrid nanoparticles (DMP) were created. D/DMP lessens the neurotoxicity and increases the water solubility of deguelin, a possible anticancer medication [57]. D/DMP nanoparticles were also added to a type of hydrogel that was sensitive to temperature changes, giving it its hydrophobic characteristics at body temperature. The new technique enhances the concentration and dwell time of deguelin in the bladder significantly [57].

1.9 Mitomycin C loaded nanoparticles:

Multiple cationic nanoparticles (NPs) were utilized to encapsulate Mitomycin C (MMC) in order to improve bladder wall penetration and tumor cell uptake. These NPs included chitosan (CS), CS coated poly - ϵ - caprolactone (CS - PCL), and PCL coated with poly - ϵ - lysine (PLL - PCL). Positive anticancer effects have been reported for these nanoconjugates [58].

1.10 Nanomaterials for the Development of Biosensors

In an attempt to lower the cost of diagnosing BC and enhance patients' quality of life by eliminating unnecessary invasive diagnostic testing, researchers discovered promising urine biomarkers for the disease [59] - [65]. Telomerase, nuclear matrix protein 22 (NMP22), cytokeratin 19, survivin, hyaluronidase (HAase), apolipoprotein A1 (ApoA1), miRNA - 21, galectin - 1 protein, etc. are possible biomarkers for the early diagnosis of BC [66]. In combination with the discovery of urinary biomarkers, biosensors have been developed that offer low detection limits, a wide linear response range, high stability, and high accuracy [67].

1.11 Applications of Nanomaterials in BC Treatment:

As previously noted, BC is regarded as one of the world's most recurrent urogenital malignancies [69]. BC is a type of epithelial carcinoma in which abnormal cells in the lining of the epithelium grow out of control. Transitional cell carcinoma (TCC), commonly known as urothelial cell carcinoma (UCC), is the most common histological class of BC [68]. Patients with BC are typically treated with a variety of techniques, such as stem cell transformation, radiation, chemotherapy, tumor resection, immunological therapy, and radical cystectomy. In order to discover more effective treatment options with fewer side effects, experts are currently doing research [70]. In general, BC is a complicated disease that exhibits great heterogeneity and multiple biological subgroups. It thus presents numerous grading and classification issues. About 70% of patients with bladder UCC develop a superficial carcinoma known as non - muscle - invasive BC (NMIBC), whereas the remaining 30% of patients develop muscle - invasive carcinoma (MIBC), which carries the risk of the tumor spreading metastatically [71]. Surgery is the most common treatment for BC, yet research indicates that after 5 years, the tumor returned in about 80% of individuals who had surgery. Chemotherapy is still regarded as the primary and crucial treatment for preventing tumours development and recurrence. While many BC patients have longer term survival thanks to chemotherapeutic medicines like taxanes, cisplatin, gemcitabine, etc., there is still a high tumour recurrence rate and significant side effects from therapeutic medications for BC therapy. Consequently, in order to improve the BC patients' quality and quantity of life, more creative and effective management is required [71]. These days, nanotechnology has significantly improved our ability to identify and cure a wide range of tumours, including that BC. Several nanoparticles (NP), including metallic, lipid, and polymeric NPs, have been employed recently to support BC therapy. A range of NP forms (Cancers 2021, 13, 2214 9 of 29) can improve the solubility of poorly soluble medicines, and multifunctional NPs exhibit good efficacy against prostate, bladder, and renal cancer. Moreover, NPs are employed as a drug delivery system (DD) to boost pharmacological effects and interactions with the urothelium. Additionally, nanotechnology can efficiently improve and enhance other contemporary technologies in conjunction with them [72]. This review aims to highlight nanotechnologies that have promise for treating breast cancer. Additionally, we will explore several nanomaterials as potential nanocarriers to mitigate adverse effects and optimize the efficacy of

chemotherapy medications, ultimately improving treatment of breast cancer.

Table 1: Applications of nanotechnology in bladder cancer [73] - [79]

Treatment Strategies	Applied NPs	Therapeutic Agents
Immunotherapy	Liposomes	BCG's CWS
Targeted therapy	GNPs	Brazilian Red Propolis (BRP), surviving
	Chitosan - SPION	5 - FU
Targeted therapy	polymeric micelle	DOX, paclitaxel
Photo thermal therapy	Polymeric NPs	DOX and IR780

2. Conclusion, Challenges, and Future Prospective

Many attempts have been made in recent decades to fight cancer by combining novel technology and traditional approaches. In this article, the applications of nanotechnology were discussed. Nanotechnology has demonstrated extensive applications both in the diagnosis and in treatment of variety of cancers, including improving the selectivity and sensitivity for the treatment of BC. NPs have been able to overcoming the limitations of current medical approaches in many research and clinical trials

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