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The Emerging Role of Chitosan-based Polymeric Nanoparticles in the Diagnosis and Treatment of Gynecological Cancers

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Abstract

Breast and gynecological cancers are the most common malignancies in females. Early-stage detection and treatment could significantly reduce the mortality rate in patients. However, common treatments such as chemotherapy and radiotherapy fail after a while and lead to recurrence and drug resistance in cancer cells. The recent use of nanotechnology has enabled the development of novel approaches for diagnosing and treating oncological diseases. Chitosan-based polymer nanoparticles (CHPNPs) with unique properties such as non-toxicity, biocompatibility, and anti-carcinogenic effects are promising tools for the clinical development of targeted delivery systems. So far, various methods have been applied to use these nanoparticles in the diagnosis and treatment of various cancers. Identifying the most practical methods is one of the most important challenges in achieving effective treatments. A review of these studies can provide better horizons to realize effective treatment. In this review, we evaluate and discuss the use of CHPNPs from published literature to assess diagnostic and therapeutic strategies in breast and gynecological cancers, including ovarian and uterine neoplasms, as well as their advantages and challenges.

Keywords: Chitosan nanoparticles, Nanotechnology, Breast neoplasms, Ovarian neoplasms, Uterine neoplasms

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Introduction

Nowadays, nanotechnology is a topic of great interest in research and medicine.[1] The study of sub-micron particles is becoming increasingly important due to their potential ability to transport drugs and target specific systems. Nanoparticle-based drugs have higher efficiency and can overcome the typical challenges of

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regular drug distribution systems.[2] Nanomedicine has the potential to facilitate precision medicines, improve therapeutic results, and reduce adverse side-effects.[3] Accurate and targeted delivery of pharmaceuticals to specific cells and tissues make them more efficacious and significantly improve outcomes.[4] Therapeutic compounds encapsulated in nanoparticles can endure longer in the bloodstream, are not easily hydrolyzed, have increased efficacy, and have greater opportunities to cross cell membranes and be taken up by cells.[5] Specific cells can be targeted by attaching special ligands to the surface of the nanodrug.[6] Among the types of nanocarriers used to transfer drug compounds, some have been studied more extensively due to their special properties and favorable results. Nanoparticles have different types, such as Lipid-based NPs, Inorganic NPs, and Polymeric NPs (Figure 1).[7, 8]

Polymeric nanoparticles are solid colloidal, rod-like, or spherical materials made of natural or synthetic materials, and by creating different structures, they display various features.[9, 10] Due to their biocompatibility and simple formulation, this nanoparticle can be a suitable means of transfer.[11] There are several methods for producing polymeric nanoparticles, each of which creates a specific product. By knowing the characteristics of each product, compatible materials (hydrophilic and hydrophobic) can be best embedded in nanoparticles and facilitate their transfer to the target cells, making polymeric NPs suitable for co-delivery uses. Drugs are dissolved, trapped, encapsulated, or absorbed in the polymer matrix composition. (Table 1).[12] Chitosan is one of the most widely used polymeric nanoparticles. It was first created in 1859 from a chitin biopolymer.[13] Chitosan is a de-acetylated form of chitin. Chitin is a natural biopolymer found in the exoskeleton of marine crustaceans such as lobsters, crabs, and the cell wall of fungi.[14, 15] Chitosan has several desirable attributes such as nontoxicity, biocompatibility, anti-carcinogenic, fungistatic, low immunogenicity, and bacteriostatic. It can interrupt

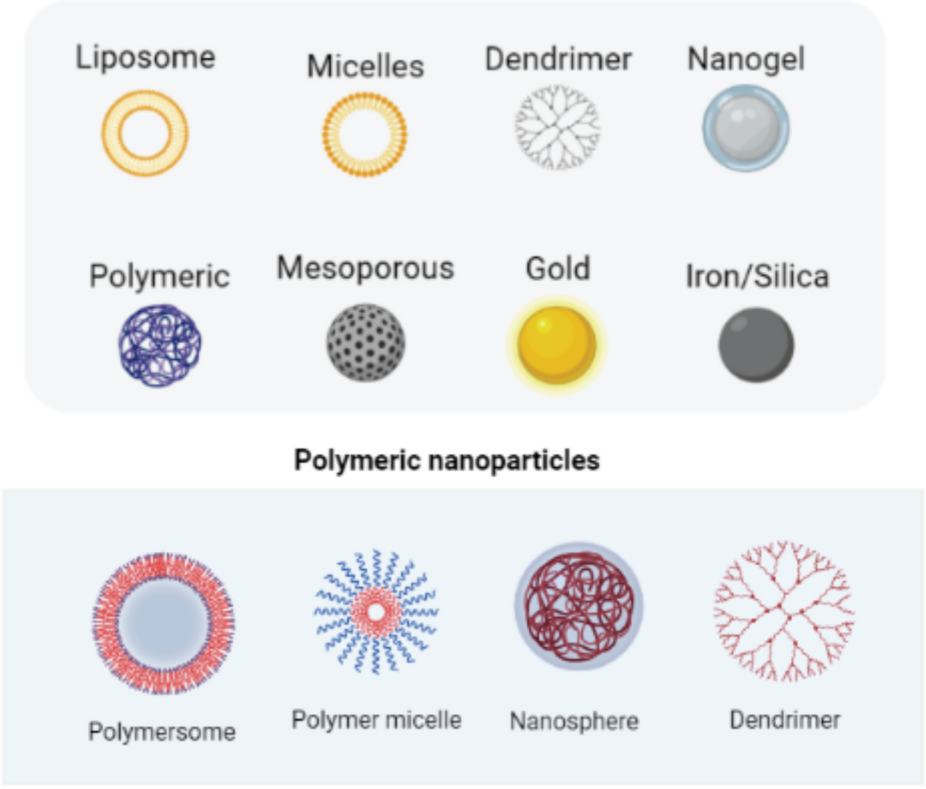

Figure 1. This figure shows the different types of nanoparticles and polymeric nanoparticles.

intercellular connections, making them more permeable.[16, 17] Chitosan is a hydrophilic polymer with one amine group and two hydroxyl groups. It can be easily attached to different functional groups by having an active amine group. The amine group causes its solubility in acidic solutions by creating a poly-electrolytic property in it. The amine groups affect a large variety of chitosan pharmaceutical and biomedical features, including mucoadhesion, penetration increment, and in situ occlusion.[5, 18] Chitosan is slightly hydrophobic due to the presence of the N-acetyl group (Figure 2).[19]

Chitosan nanoparticles preparation methods

There are several ways to create chitosan nanoparticles, and the method of preparation is a key step in ensuring that the particulates behave as intended,[20, 21] playing a vital role in achieving the desired properties. Ionic gelation, emulsion cross-linking, spray-drying, emulsion droplet coalescence method, nanoprecipitation, reverse micellisation method, desolvation/simple coacervation / phase separation, modified ionic gelation with radical polymerization, and emulsion solvent diffusion are some prevalent methods.[12, 22] It should be noted that certain characteristics of chitosan-mediated drug delivery systems, such as particle size, toxicity, different interactions of chitosan nanoformulation and drugs, thermal and chemical stability, and kinetics, strongly depend on the selected preparation methods.[23]

The surface of chitosan-based polymeric nanoparticles can be easily altered to target specific tissues. Thus, the use of these nanoparticles as a cell-specific targeting system can prevent non-specific interactions, side-effects, and toxicities of drugs.[24] In addition, specific biomarkers can be conjugated to chitosan for more precise detection and imaging of malignancies.[25, 26] Nevertheless, it is worth noting that the challenges of polymeric nanoparticle application are an increased risk of particle accumulation and low toxicity in some cases.[27] Currently, only a limited number of polymeric nanomedicines are FDA approved and applied in the clinic, but different types of polymeric nanocarriers are now undergoing investigation in many clinical trials.[28]

Table 1. Method of preparation of Chitosan-based polymeric nanoparticles

Method of preparation of CSNPs
Ionic gelation/polyelectrolyte complexation
Emulsion droplet coalescence
Emulsion solvent diffusion
Reverse micellisation
Desolvation
Modified ionic gelation with radical polymerisation
Emulsification cross-linking
Nanoprecipitation
Spray-drying

CSNPs: Chitosan-based polymeric nanoparticles

Gynecological cancers

Female-specific malignancies (FSMs) such as breast cancer (BC), ovarian cancer (OC), and uterine cancer (cervical cancer and endometrial cancer) have a profound effect on the health of women worldwide and play a significant role in the global cancer burden.[29, 30] Each type of female-specific cancer has unique epidemiological and genetic risk factors, symptoms, prognosis, and response to therapy, and they cannot be easily diagnosed or treated.[31] The prevalence of these

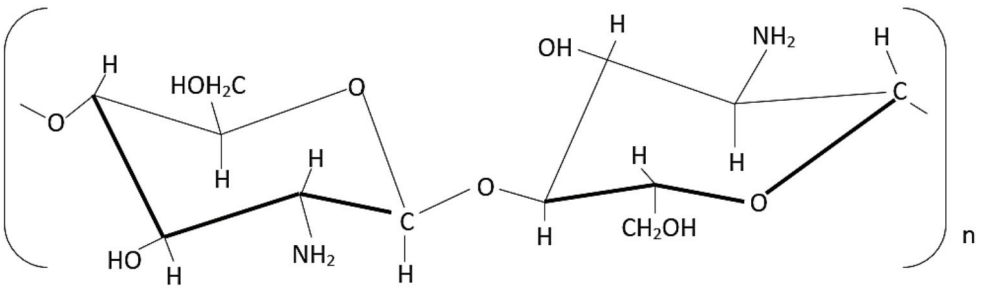

Figure 2. This figure depicts the chitosan chemical structure.

Table 2. Biological ligand in breast and gynecological cancer

Biomarker	Technology used for discovery	Type	Type of cancer
RS/DJ-1	Serum profiling	Serum protein	BC
CA125			EC/OC
CA15-3			BC/OC
Ca19-9			EC/OC
CA27-29			BC
Gal-3			OC
CA72.4			OC
HER-20			BC
HE4			EC/OC
P53	Humeral response	autoantibody	BC
p16			VC
CYFRA21-1			UC
HSP60			BC
SCC-Ag			CC
HSP90			BC
MUC1			BC
α-2-HS-Glycoprotein	Nipple aspirate fluid profiling	Ductal protein	BC
Lipophilin B			BC
β-Globin			BC
Hemopexin			BC
Vitamin D-binding			BC
protein			BC

BC: Breast cance; EC: Endometrial cancer; OC: Ovarian cancer; UC: Uterine cancer; VC: Vulvar cancer; CC: Cervical cancer

cancers is such that, by 2020, it was estimated that more than 3 million new patients and more than 1 million cancer deaths worldwide. Most gynecological diseases are associated with infertility, which causes chronic stress and various psychological problems, adversely affecting the normal life-style of families and burdening the health of society. With the physical and mental comfort of fertile women, the family can be a more suitable platform for the growth and education of children, and healthier children will be delivered to society.[32-34] Innovating new

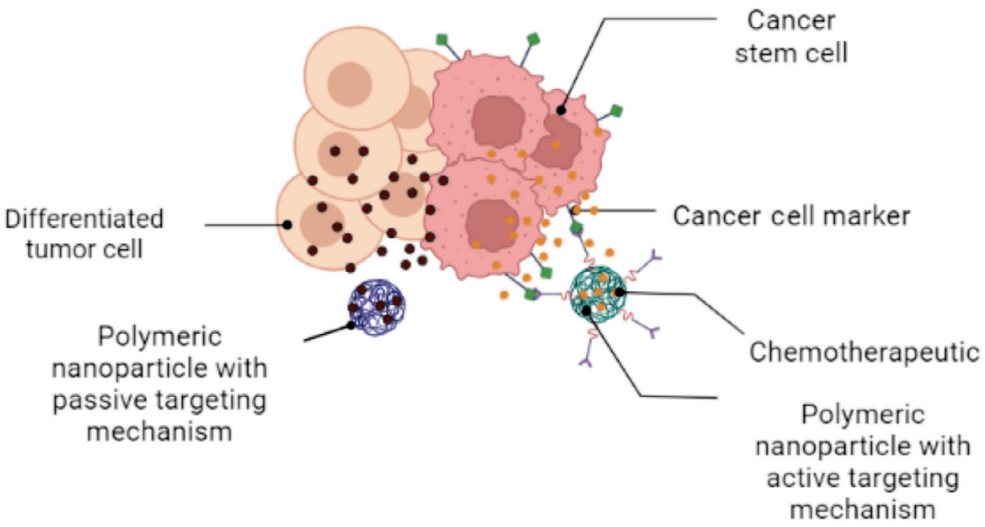

Figure 3. In this drug delivery system, drug targeting is performed by identifying the target agent that binds to the receptors on the target cells at the level of the drug delivery system. The target group includes bioadhesive nonionic surfactants,

Table 3. Uterine serous and clear cell carcinomas are rare but more metastatic and related to a poor prognosis. Uterine sarcomas contain 2 to 5% of uterine malignancies and emerge from the myometrium or other mesenchymal structures

Gynecologic oncology group classifications of uterine sarcomas
Non-epithelial tumors
Endometrial stromal tumors
Stromal nodule (benign)
Endometrial stromal sarcoma
Undifferentiated endometrial sarcoma
Leiomyosarcoma
Myxoid
Smooth muscle tumors of uncertain malignant potential
Mixed endometrial stromal and smooth-muscle tumors
Mixed epithelial-non-epithelial tumors
Adenosarcoma
Homologous
Heterologous
Adenosarcoma with high-grade overgrowth

methods of diagnosis and treatments that can potentially improve the therapeutic outcome for cancer patients is much needed. In this review, we focus on current documents for the efficacy of CHPNPs and their new applications in the diagnosis and treatment of female-specific cancers.

Biological ligands in breast and gynecological cancer

Lately, much attention has been paid to the identification of biological markers for use as indicators of disease activity, as well as prognostic factors and predictors of survival, recurrence, and treatment response in female patients. There are various markers for breast and gynecological cancer diagnosis. DNA biomarkers provide information on the process of tumor formation, but they are related to poor early diagnosis because of low concentrations of cancer markers. Serum tumor biomarker assessment is a strategy to evaluate tumor presence, recurrence, or response to treatment in gynecological cancer patients.[35, 36] Protein biomarkers are the main index of BC, which can be arranged as two main markers. Predictive protein markers provide information on a certain treatment intervention, while prognostic protein markers suggest general information on the issues (Table 2).[37]

OC

OC is the 8th leading cause of cancer mortality in women.[38] Due to the lack of clinical symptoms, it is often diagnosed too late in advanced stages (stage III and IV). OC includes four stages: stage 1 is limited to one or both ovaries, stage 2 spreads to pelvic viscera (bladder, uterus, ovarian tubes, or rectum), stage 3 extends to the abdominal lining, abdomen, and lymph nodes, and finally, stage 4 spreads to abdominal organs (liver, intestine, and spleen), and even the lungs in the thoracic cage may be involved. Tumor cells' metastasis into the peritoneal cavity significantly reduces the chance of treatment.[39-41]

Diagnosis

There are some trials for early disease diagnosis, such as clinical histories, physical examination, tissue biopsy, ultrasound assessment, positron emission tomography (PET), and computed tomography (CT) scan. An efficient method for early detection of OC is to evaluate cancer antigen-125 (CA-125) serum protein that rises in 80% of women with OC. In other words, an increase in serum CA-125 is a sign of treatment failure.[42, 43] Circulating tumor DNA evaluation is a novel specific technique that is being used recently that can precisely diagnose tumor cells and malignancy.[44] Lysophosphatidic acid is another option for assessment in women with benign gynecologic diseases.[45]

Treatment

Surgery, radiation therapy, and chemotherapy have additional benefits on survival.[46] Current shreds of evidence indicate that OC cells are relatively resistant to classical chemotherapy, and there has been only an approximate improvement

Table 4. Endometrioid adenocarcinoma arises from the endometrium and is the most common pathologic subtype (95% of cases)

Classifications of endometrial carcinomas
Endometrial adenocarcinoma
Adenocarcinoma with squamous differentiation
Villoglandular
Secretory
Ciliated cell
Uterine serous carcinoma
Clear cell carcinoma
Mucinous carcinoma
Carcinosarcoma
Squamous cell carcinoma
Mixed adenocarcinoma and other rare variants

in the overall survival of OC patients. [47] Overall, in these patients, most treatment strategies have led to a high rate of relapse and poor outcomes that required more endeavors to advance beneficial therapeutic methods.[48]

Nanotechnology has an important impression on the diagnosis and treatment of OC.[49] In chemotherapy, the manufactured nanosystem must have significant drug loading capacity, drug dissolving capacity in the inner core, and selective aggregation in target tumor tissue through the effects of permeability and retention. In addition, the development of specific ligand-functionalized nanoforms will enable special targeting of ovarian tumors and ultimately increase therapeutic potential compared with non-functional counterparts.[50-52]

Chitosan-based nanostructured units have been highly used for effective delivery of biomolecules and macromolecules, including nutrients, proteins, vitamins, phenolic, and hydrophobic drugs in diverse biological systems.[53] S´anchez-Ramírez et al. designed a biocompatible and biodegradable nanocarrier system based on chitosan (lactic-co-glycolic) (PLGA) synthesized CP-ICG NPs for competitive trapping of photoactive drugs and chemotherapy (CP), and its potential for anti-cancer activity was evaluated. These nanoparticles showed cytotoxic and antitumor effects on the SKOV3 OC cell line after irradiating the cells with an 800 nm laser.[54]

Recently, curcumin loaded on poly lactic-hemaglycolic acid (PLGA), a biodegradable nanoparticle (CUR-NP), was tested against SKOV3 human ovarian adenocarcinoma cells by photodynamic therapy. Increased stability was observed compared with free curcumin and also showed strong apoptosis.[55] Pakchin et al. has developed an immune-based electrochemical nanosensor to identify CA-125. This nanosensor was designed based on polyamidoamine/gold nanoparticles and 3D reduced graphene oxide/multiwall carbon nanotubes nanosensor. In order to increase the conductivity and the number of antibodies (Abs) immobilized on the electrode outward, Polyamidoamine/gold nanoparticles (PAMAM/AuNPs) were used. Toluidine blue and antibody appended to O-succinyl-chitosan-magnetic nanoparticles (Suc-CS@MNPs) as a detector. They improved the insignificant solubility of chitosan with succinic anhydride, applying a novel rectification technique. The reliability of the constructed nanosensor in detecting CA-125 was verified by standard addition recovery method.[56]

OC frequently spreads to peritoneum and causes enormous aggregation of fluid (ascites). By isolating and analyzing cancer cells in ascites, unique and valuable information would be yielded. M. Castro et al. designed an ascites-specific microfluidic chip (ATC chip) that extracts ATCs from their profoundly inflammatory microenvironment. It's a simple and rapid ATC profiling approach that has the potential to expand the reach of point-of-care strategies and lead therapeutic clinical trials for OC.[57] Jia Xu et al. encapsulated hydroxyapatite nanoparticles and marizomib with chitosan to increase marizomib's

Table 5. Application of chitosan-based nanoparticles in the drug delivery system in preclinical and clinical studies

A substance used in integration with chitosan nanoparticles	Research findings	Reference
Preclinical research		
Curcumin	Increased Curcumin's anticancer activity against colon and breast cancer cells	(139)
Insulin	Decreased glycaemia was observed in diabetic rats	(140)
Marizomib	Increased absorption by cancer cells, induced apoptosis, and destroyed ovarian A2780 cancer cells	(141)
Raloxifene	Induced more apoptosis in breast cancer cells	(91)
Theophylline	Anti-inflammatory effects were noticeably enhanced	(142)
Paclitaxel	Significant inhibition of tumor progression and long survival	(136)
Clinical research		
Doxorubicin	Decreased Doxorubicin toxicity and tumor growth rate	(143)
Morphine	Improved morphine pain relievers	(144)

(Salinosporamide A. is an anticancer agent) efficacy and bioavailability. The created nanoparticles were efficaciously absorbed by cancer cells, induced apoptosis, and destroyed ovarian A2780 cancer cells.[58]

BC

BC is the leading cause of cancer death among women aged 20 to 59. In 2021, an estimated[59] 281,550 new cases of ductal carcinoma in situ (DCIS) of the female breast were reported. The incidence of BC continues to rise at about 0.5% per year.[60] BC can be categorized according to the molecular subtypes as luminal (A&B), human epidermal growth factor receptor 2 (HER2), and estrogen (ER) / progesterone receptor (PR) positive and triple negative.[61] Nearly 70% of all reported cases among all recognized subtypes are ER/PR positive subtypes.[62] Approximately 20% of BCs do not express HER2, ER, and PR, which is known as triple-negative (TN), and is basal-like (about 75%) and has an aggressive phenotype with a higher rate of metastasis.[63] The main cause of BC death has been reported to be the result of possible metastasis to distant organs such as the liver, lungs, lymph nodes, bones, and brain.[64]

Diagnosis

The most prevalent histopathology of BC is invasive ductal carcinoma (50%-75% of patients), followed by invasive lobular cancer (5%-15% of patients).[65] Identifying cancer cells in the early stages is the key to a better prognosis. The initial diagnosis involves self and clinical examination and radiographic scans (mammography, magnetic resonance imaging, ultrasound, CT, PET, microwave imaging) followed by invasive biopsy for the histological confirmation of invasive disease.[66-69] BC can also be diagnosed by biomarker-based methods such as radioimmunoassay, immunohistochemistry, enzyme-linked immunosorbent assay (ELISA), and fluoroimmunoassay. Some biomarkers are shown in table 2. Another new method for sensitive detection of cancer cells is optical biosensors, including fiber optics, fluorescence, resonant mirror sensors, interferometry, and surface plasmon resonance, which have been developed to detect target cancer markers.[70, 71]

Treatment

To increase the survival rate in cancer patients, the development of effective therapies against metastatic BC remains an important priority. The main purposes of treatment for non-metastatic BC, are to eliminate the tumor from the breast and associated lymph nodes to prevent metastatic

recurrence.[72-74] Routine treatment for non-invasive BC consists of lumpectomy, mastectomy, sampling, or removal of axillary lymph nodes, with consideration of postoperative radiation. Depending on the cancer subtype, systemic treatment (endocrine therapy for all HR+, trastuzumab-based ERBB2-directed antibody therapy plus chemotherapy for all ERBB2+ tumors, and chemotherapy alone for triple-negative BC is also applied.

For invasive BC, therapeutic targets are to increase life expectancy and relieve symptoms. Presently, invasive BC is incurable in almost all patients. The same basic categories of systemic therapy are used in invasive BC.[75-79]

Among all kinds of treatments, chemotherapy is commonly used for treating BC. Most cancer cells can be eliminated by efficient chemotherapy throughout the body. There are some approved anticancer medications such as tamoxifen, taxanes, paclitaxel, docetaxel, doxorubicin, raloxifene, and methotrexate used for the treatment of BC.[80, 81] However, the low bioavailability and poor aqueous solubility of these drugs have led to reduced treatment efficiency.

Two main strategies for better therapeutic efficacy and reducing chemotherapy side-effects are tumor-targeted delivery and managed release of these medications through nanoparticles. Drug-loaded nanoparticles compared to conventional chemotherapy drugs are considered a favorable tool for cancer treatments because of their high loading capacity, stability, specificity, tolerability, and reduced toxicity. The delivery system is designed to keep the therapeutic intact until it arrives at the desired location without any changes. Nanoparticles can actively and passively deliver anticancer drugs to cancerous tumors during treatments (Figure 3). Among different kinds of nanoparticles, polymeric nanoparticles (chitosan), liposomes, micelles, solid lipid nanoparticles, and gold nanoparticles are commonly used in the treatment of BC.[82, 83]

Due to their positive charge, chitosan nanoparticles (CHNPs) have great potential as a means of drug delivery that enables them to be transported across cell membranes and in sequential endocytosis.[84, 85] Their mucoadhesive attributes help in disentangling the epithelial tight junctions, which makes CHNPs suitable for oral administration.[86, 87] In addition, the presence of a free amino group facilitates CHNPs with targeting ligands for active targeting. Conjugated ligand CHNPs get away endo-lysosomal section and aggregate cytoplasm due to receptor-mediated endocytosis and release the drug for a longer period of time.[88-90] A. Yadav et al. (2020) produced a stable combination of raloxifene-encapsulated CHNPs and RGD-CHNPs by non-toxic ionic gelation. pH-dependent research revealed that nanoparticles have more stability, zeta potential, and cellular uptake at acidic pH (as in solid tumors) in comparison with physiological pH. RGD combination enhances in vitro cellular absorption of CHNPs in $\alpha v\beta 3$ integrin-expressing BC cells and induced more apoptosis in BC cells that was further augmented by lower pH. Furthermore, Rlx-RGD-CHNPs obviously inhibited the migration and angiogenesis in BC cells.[91] Z. Shakeran et al. (2021) developed a novel method to produce biodegradable mesoporous silica nanoparticles (MSNs) with tiny and identical particle sizes, achieve high methotrexate (MTX) loading through covalent amine and chitosan-functionalization, monitor cell uptake, and display the potential for reduced BC cell viability at low doses.[92] In their research, magnetic alginate/chitosan nanoparticles were created with curcumin loading to increase the bioavailability, uptake ability, and cytotoxicity of curcumin to human Caucasian BC cells (MDA-MB-231). They deposited alginate and chitosan on Fe3O4 magnetic nanoparticles based on their electrostatic attributes. The curcumin had sustained release by changing the number of layers of chitosan and alginate on the nanoparticles. The MTT assay and FACS assay indicated that the curcumin-loaded nanoparticles demonstrated significantly more cytotoxicity towards MDA-MB-231 cells than HDF cells.[93]

Uterine Cancer

Malignancy originating from endometrial glands is known as carcinoma, compared with the rare uterine sarcoma that originates in

mesenchymal tissues such as smooth muscle or connective tissue.[94] There are two types of endometrial cancer. Type I is more prevalent, making up more than 70% of cases. This kind of cancer is related to unopposed estrogen incitement and is known as endometriosis adenocarcinoma, which are some low-grade tumors. Type II tumors are more probable to be high grade, with a poor prognosis and a high risk of recurrence and metastasis. Only 10% of uterine cancers account for type II, which accounts for 40% of related deaths.[95, 96]

It was estimated that there were 14,480 new cases of uterine cervix cancer and 66,570 new cases of uterine corpus cancer in 2021. Uterine cancer (cervix and corpus) is the second most common gynecologic cancer among women in terms of incidence and mortality worldwide in 2021.[59,97, 98] Endometrial cancer is less common in premenopausal females, and most cases occur in women over 50 years of age.[99] Estrogen exposure during life is the basis of most risk factors. Early menarche, late menopause, obesity, and estrogen-generating tumors are related to an expanded risk of endometrial cancer. Prolonged estrogen exposure is a significant risk factor, causing incessant endometrial growth. As cells proliferate, the probability of mutations and endometrial cancer increases.[100-103] Nulliparity has a significantly worse prognosis.

During pregnancy, progesterone is the dominant hormone, and pregnancy-related agents may affect the biology of endometrial epithelial cells.[104] Research has shown that the risk of endometrial cancer increases in patients treated with tamoxifen, a selective estrogen receptor modulator used for BC treatment.[105, 106] Lynch syndrome, the most common hereditary colorectal carcinoma, and polycystic ovary syndrome increase the risk of uterine cancer to a great extent. Meanwhile, some more protective factors were noted in research, such as full-term pregnancy, breastfeeding, contraceptives, physical activities, alcohol, and smoking.[107-110] Tables 3 and 4 classify endometrial carcinomas and sarcomas.[111]

Diagnosis

There are some common clinical manifestations for early detection of endometrial cancer. The main early symptom for women diagnosed with endometrial cancer is irregular uterine (vaginal) bleeding. About 80% of women with endometrial cancer experience abnormal uterine bleeding.[112, 113] Nevertheless, menometrorrhagia and extended cycles of amenorrhea (≥6 months) after the age of 45 years should be evaluated. A significant percentage of endometrial cancers occur between ages 45 and 64 years. All postmenopausal bleeding should be monitored, especially if there are risk factors for endometrial hyperplasia or cancer.[114] Women who exhibit the above symptoms should undergo abdominal, speculum, and pelvic exams. Women older than 45 years should undergo endometrial sampling. Medical, family, and surgical history may be related to the disease.[115] Diagnosis of endometrial cancer under the age of 45 is rare. Unusual cervical cytology may be the first clue to uterine cancer, but it is not very accurate. Based on age, symptoms, and the presence of risk factors, endometrial evaluation is recommended.[111] The most appropriate diagnostic plan in cases with probable endometrial cancer is still controversial. There are some assessments available for investigating probable endometrial cancer, such as transvaginal ultrasound scanning (TVS), hysteroscopy, and endometrial biopsy.[116] TVS is an accurate, non-invasive, available, and cost-effective method that examines the thickness of the endometrial layer.[117] Ultrasound results indicate biopsy indication due to endothelial thickness.[118] The thickness of the endometrium should be 4 mm or less for a normal transvaginal ultrasound result. Following ultrasonography, saline infusion sono-hysterography can also be applied to assess the endometrium to obtain better images of structural alterations, especially when cases have polyps, submucosal fibroids, and endometrial hyperplasia. Extra information about endometrial thickness and irregularities and abnormalities may be provided by magnetic resonance imaging.[119] The uptake pattern in the tumor site by fluorodeoxyglucose PET can be detected in different kinds of tumors.[120] Nevertheless, the decisive diagnosis of endometrial carcinoma is by histological

biopsy.[115] Hysteroscopy is usually indicated for patients at high risk for endometrial cancer and cases in whom outpatient biopsy was insufficient or unable. Hysteroscopy can detect endometrial polyps and other ultrasound irregularities. A positive result in hysteroscopy increases the risk of cancer, while a negative result in hysteroscopy decreases the risk of cancer.[121] In uterine carcinoma diagnosis, specific factors have a little role. In part of the sarcomas, CA125 elevates, and in part of leiomyosarcoma, lactate dehydrogenase levels raise so that it is not very practical.[122, 123]

Treatment

Recently, minimally invasive surgery has been applied for surgical staging in cases with endometrial cancer.[124] Cases with metastatic conditions should undergo more aggressive surgery called radical hysterectomy, which involves the removal of the uterus, cervix, parametria, and upper vagina.[125] Based on the stage and existence of risk factors, the treatment of endometrial cancer after surgery continues. Cases are categorized into low, intermediate, and high-risk groups, and based on the risk rate, adjuvant therapy is done.[126, 127]

For adjuvant therapy, radiation therapy is a common method for preventing local recurrence. In high-risk cases, besides radiotherapy, chemotherapy (carboplatin and paclitaxel) accompanied by a considerable diminution in recurrence rate.[128] PORTEC-2 trial corroborates that vaginal brachytherapy is a standard adjuvant therapy for cases with high-intermediate recurrence risk.[129] In early-stage endometrial serous cancer, platinum-based chemotherapy in combination with bevacizumab, a VEGF inhibitor, as first-line adjuvant treatment is advised.[130, 131]

Nanotechnology is being used clinically to boost therapeutic indexes of chemoradiotherapy. Paclitaxel nanoparticle albumin-bound (nab), a new authorized particle-based chemotherapeutic, is recently being evaluated following its simultaneous prescription with radiotherapy in many chemoradiotherapy clinical trials (Phase III) in endometrial and cervical cancer.[132] Nano-based methods have demonstrated affirmative outcomes in these therapeutic areas.

A parallel therapeutic system to decrease the tumor conformity of a radiotherapy-resistant cell niche, boosted chemo-radiotherapeutics, boosted PET-CT contrast for designing/assessing response, and in vivo image contrast background to help image-guided therapies remain critical necessities.[133] Lately, a novel Nano self-assembled core-shell system micelle made by low molecular weight carboxymethyl chitosan and α-tocopherol succinate has been generated. The maximum tamoxifen load of the system can reach 8.08 ± 0.98%. The consistency of the system has been shown and the bioavailability has increased by 1.9-fold in comparison with that with free drug molecules.[134]

Some studies have applied folic acid combined with chitosan to generate nanocarriers to improve the drug loading performance and the bioavailability of chitosan. C. Misra et al. made tamoxifen practicable folic acid chitosan nanoparticles, where drug attaching is created by H-bonding, van der Waals bonding, and hydrophobic links. They have shown that as the measure of the nanocapsules elevated, a more firm drug-polymer bond was made, and TAM was more efficient.[135]

In a xenograft model of endometrial cancer, K. Ebeid et al. generated more lethality to paclitaxel (the first treatment for endometrial carcinoma) in cells with mutant p53 and increased the therapeutic effects applying polymeric nanoparticles. P53 observes checkpoints in the cell cycle as a supervisor of the genome, allowing cells to correct the damaged DNA or cause apoptosis. They prepared a composition of paclitaxel-loaded nanoparticles with the antiangiogenic molecular suppressor BIBF 1120 for amplifying the lethality specifically. Treatment resulted in significant inhibition of tumor progression and long survival.[136]

Chitosan-based polymeric nanoparticles application in pre-clinical and clinical research

Scientific studies have provided promising results from chitosan nanoparticles in anticancer drug delivery and cancer treatment. Nanodrug delivery systems based on CHPNPs have been developed for preclinical and clinical research.[137]

In this article, CHPNP's preclinical and clinical applications for recognition and cancer treatment will be discussed due to their less systemic toxicity and more cytotoxicity against cancer cells and tumors. Because of their specific characteristics, their applications include oral delivery, ocular drug delivery, nasal drug delivery, pulmonary drug delivery, mucosal drug delivery, gene delivery, vaccine delivery, vaginal drug delivery, and cancer treatment. Some of these studies are listed in table 5.

Conclusion and Future Perspective

Gynecological and BCs are the most important malignancies in women, negatively affecting the lifestyle of families and leading to many other ailments. Finding ways for early diagnosis and treatment can be a turning point in the fight against these cancers. Cancer cells could be detected and treated more efficiently by using nanotechnology. Novel drug delivery systems provide many promising methods to the challenges faced by kind of cancer treatment. In the treatment of gynecological cancers, nanocarriers help deal with challenges of low aqueous dissolution of chemotherapeutic medicines and more precise targeting either by active or inactive targeting, hence reducing adverse side effects. Chitosan-based polymeric nanoparticles are a favorable source for co-delivery of chemotherapeutic combinations for gynecological cancers. Drug resistance and cancer recurrence will be eliminated by using nanochemotherapeutics. According to the current review, nanotechnology provides many promising methods to the challenges faced by current cancer detection and treatment. In the treatment of cancers, nanocarriers help deal with challenges of low aqueous dissolution of chemotherapeutic medicines and more precise targeting either by active or inactive targeting, hence reducing adverse side effects. Chitosan-based polymeric nanoparticles have a new perspective for combined treatment strategies against cancers. They are a favorable source for co-delivery of chemotherapeutic combinations for selective treatment. Innovative therapeutic methods are made with the application of nanotechnology. Advances in early diagnosis and efficient noninvasive therapy in many types of cancers by applying nanotechnology have created clear horizons of increasing the chances of survival rate in these diseases. The use of chitosan nanoparticles in the diagnosis and treatment of gynecological cancers has yielded promising results, and further research in the clinical context is needed to precisely evaluate their effectiveness. It should be our constant effort to fight for the definitive cure and more survival advantages.

Conflict of Interest

None declared.

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