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"Adverse Drug Reaction in Uterine Cancer: A Review of Therapeutic Challenges"

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ABSTRACT
Uterine cancer, mainly endometrial carcinoma, poses an increasing clinical challenge because of its surging incidence and complicated treatment options. Treatment protocols—such as chemotherapy, radiation therapy, and targeted immunotherapy—have greatly enhanced survival rates but often come with considerable side effects. In individuals treated with lenvatinib and pembrolizumab, frequent adverse effects consist of hypothyroidism, hypertension, fatigue, diarrhea, and musculoskeletal issues, with grade 3–4 incidents like significant fatigue and weight loss appearing in more than 10% of patients. Radiotherapy, especially for high-risk patients, is linked to gastrointestinal and genitourinary toxicities, and its adverse effects are worsened by factors like age, obesity, lymphovascular space invasion (LVSI), and postponement of treatment initiation2. Additionally, stereotactic pelvic adjuvant radiation therapy has demonstrated acute gastrointestinal and genitourinary toxicities, affecting patients' quality of life even with its therapeutic effectiveness. To effectively handle these negative reactions, proactive monitoring, educating patients, and strategic dose adjustments are needed to weigh treatment advantages against tolerability.

KEYWORDS: Cancer, uterine cancer, endometrial cancer, cancer treatment adverse effects, adverse drug reactions (ADR),risk factors, pathophysiology, treatment-related morbidity

I. INTRODUCTION

Uterine cancer, the predominant pelvic gynecologic malignancy in developed nations, denotes any invasive tumor of the uterine corpus, primarily consisting of endometrial carcinomas. Around 67,880 new cases are identified each year in the U.S., leading to 13,250 fatalities, ranking it as the fourth most prevalent cancer in women. Endometrial adenocarcinoma represents approximately 95% of these instances and usually exhibits postmenopausal bleeding, leading to timely medical assessment. This results in a significant percentage of early-stage diagnoses (stage I) among 70–75% of patients and supports a positive outlook, as endometrial adenocarcinoma accounts for merely 4% of cancer fatalities in women. Conversely, uterine sarcomas are less common (accounting for under 9% of uterine cancers) yet display a more aggressive nature and a worse outlook. Histological varieties of endometrial carcinoma comprise endometrioid (approximately 80%), adenosquamous, clear cell, and papillary serous classifications. Sarcomas comprise carcinosarcomas (48–50%), leiomyosarcomas (38–40%), and endometrial stromal sarcomas (8–10%), alongside uncommon heterologous types such as rhabdomyosarcomas and osteosarcomas. Even though it is common, no screening tests are advised for women without symptoms, since recognizing symptoms early and taking prompt action leads to high survival rates [1].The growing prevalence of endometrial cancer, especially in wealthy Western countries, primarily because of escalating obesity levels. The illness is divided into two primary categories: Type I, which is the more prevalent form, dependent on estrogen, usually affects overweight postmenopausal women, and has a generally positive outlook; and Type II, which is rarer, affects younger and slimmer women, and is marked by aggressive histological variants such as serous or clear cell carcinoma, resulting in a less favorable outcome. Because the majority of endometrial cancer cases show symptoms early, screening in the general population is not economically feasible. Surveillance can be advantageous for individuals at high risk, such as those with certain genetic syndromes (e.g., Lynch syndrome, Cowden's), a past of breast cancer, hormone replacement treatment, or prolonged tamoxifen use. Surgery is the primary method of treatment, generally consisting of a total hysterectomy along with bilateral salpingo-oophorectomy, even when the adnexa look normal, because of the potential for micrometastases. The effectiveness and safety of laparoscopic surgery are being examined, pending findings from the LAP-2 study conducted by the Gynaecologic Oncology Group. Post-treatment follow-up procedures differ but typically include

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regular monitoring every 3–4 months at first for high-risk patients, then every six months for up to five years to identify recurrences quickly [2].Uterine-origin smooth-muscle tumors, especially leiomyomas, comprise a varied set of neoplasms, with leiomyomas being the most prevalent and usually sensitive to hormones. Their development is frequently associated with the levels of estrogen and progesterone receptors. Leiomyomas may experience different degenerative alterations, with hyaline degeneration being the most common and significant because it can be confused with cancer. Red degeneration, frequently linked to pregnancy, may result in pain and fever. Therapies like gonadotropin-releasing hormone analogs or selective arterial embolization may result in considerable alterations in these tumors. Variants such as cellular and symplastic leiomyomas necessitate precise diagnosis to prevent misidentification with sarcomas. Moreover, two uncommon non-cancerous types benign metastasizing leiomyoma and disseminated peritoneal leiomyomatosis develop outside the uterus, remaining non-malignant, while ongoing studies explore their hormonal and developmental mechanisms. Conversely, leiomyosarcoma, although infrequent, is a significant cancer that necessitates focus on necrosis, cellular atypism, and mitotic activity for precise diagnosis. This data is featured in the journal Environmental Health Perspectives (EHP), a prestigious, peer-reviewed outlet backed by the NIEHS, concentrating on the environmental influences on human health and achieving high rankings in various scientific fields [3].This cross-sectional cohort study examined the enduring effects of various treatment methods on quality of life (QoL) in uterine cancer survivors who were treated at MD Anderson Cancer Center from 2006 to 2017. A total of 309 women participated in a survey utilizing the validated Functional Assessment of Cancer Therapy Endometrial (FACT-En) questionnaire, which evaluates quality of life across physical, social, emotional, functional, and endometrial cancer-specific areas. Participants were divided into four groups: those receiving surgery only (n=64), surgery plus brachytherapy (n=77), surgery with external beam radiation therapy (EBRT; n=96), and a non-cancer control group that had a hysterectomy for non-malignant conditions (n=72). The average duration from the operation to the completion of the survey was 6.7 years. In general, QoL varied considerably across cohorts (P=0.006), with the EBRT cohort indicating the lowest average FACT-En score (139.4) and the brachytherapy cohort the highest (150.6). In a similar fashion, for endometrial-specific QoL, the EBRT group once more recorded the lowest scores (53.5), whereas the brachytherapy group achieved the highest (57.5; P=0.007). These results indicate that the type of treatment significantly influences QoL, with EBRT linked to more enduring negative effects, while brachytherapy seems to maintain QoL better. The research highlights the significance of choosing the right treatment in survivorship planning, especially for women needing adjuvant therapy for endometrial cancer [4].The rising prevalence of uterine cancer, especially in wealthy Western nations, primarily as a result of escalating obesity levels. It classifies the illness into two forms: Type I, which is more prevalent and generally impacts obese postmenopausal women, and Type II, seen in younger, leaner women and marked by more aggressive, non-estrogen-dependent tumors such as serous or clear cell histologies. Since the majority of patients show symptoms and have early-stage disease, regular screening is deemed not cost-effective for the general population, although monitoring could help high-risk groups. This encompasses people with a family background of endometrial cancer, previous hormone replacement therapy lacking adequate progestogens, tamoxifen usage, hereditary conditions like Lynch syndrome, Cowden's, and Peutz-Jeghers, along with individuals who are obese or have a history of breast cancer. Surgery continues to be the fundamental treatment approach, usually requiring a total hysterectomy with bilateral salpingo-oophorectomy, and the extraction of the adnexa is recommended even if they look normal because of the chance of micrometastasis. Although laparoscopic methods are being investigated, their safety and effectiveness remain under assessment, awaiting findings from the Gynecologic Oncology Group's LAP-2 trial. Ongoing care for patients at high risk typically requires regular monitoring every 3 to 4 months at first, reducing to twice a year to identify any recurrence early over a span of five years [5] .The Swedish Council for Health Technology Assessment (SBU) regarding the significance of radiation therapy in treating uterine cancer. Utilizing information from 10 scientific investigations comprising one randomized trial, two prospective studies, and seven retrospective studies the review encompasses a total of 3,446 individuals. These results are compared with an earlier 1996 review that encompassed 13,597

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individuals. The assessment finds that adjuvant radiotherapy is typically not needed for patients with low-risk uterine cancer, since it does not enhance survival rates. Nonetheless, in high-risk patients, although radiotherapy aids in lowering relapse rates, it still does not notably impact overall survival. Moreover, substantial evidence backs the application of radiotherapy as a curative option for patients who cannot undergo surgery and those experiencing localized recurrences. The article emphasizes the intricate function of radiotherapy in uterine cancer, supporting a more customized strategy based on the patient's risk assessment and eligibility for surgery [6].A two-pronged model: Type I (estrogen-driven, low-grade, endometrioid tumors linked to obesity and metabolic syndrome) and Type II (high-grade, non-endometrioid tumors exhibiting a more aggressive clinical trajectory). Though this model has significantly influenced clinical comprehension, education, and research, new molecular, pathological, and epidemiological data have shown that endometrial cancer is much more diverse than the initial two-category framework indicates. The Cancer Genome Atlas (TCGA) currently classifies endometrial cancer into four molecular subtypes according to mutation profiles and histological characteristics, illustrating a more intricate disease biology. Moreover, metabolic conditions such as obesity and hormonal effects seem significant for all histologic types, not only Type I. While Bokhman's classification continues to be helpful for general groupings and in situations with limited data, present clinical and research methodologies increasingly require the combination of molecular, pathological, and clinical information for a more accurate and individualized comprehension of endometrial cancer[7]. Utilizing clinical data from the UPMC Network Cancer Registry, the researchers employed logistic regression to assess variations between 176 women with Type II EC and 1,576 with Type I EC. The results showed that women diagnosed with Type II EC were considerably more probable to be older, of non-white ethnicity, and have a background of other primary tumors. Conversely, they were less prone to obesity than individuals with Type I EC. These findings underscore the unique etiological characteristics of the two EC subtypes, indicating that Type II EC is a more aggressive variant of the disease with worse outcomes and may require alternative preventive and treatment approaches. The research highlights the necessity for additional studies to enhance the understanding and management of risk factors related to Type II EC [8] .the molecular differences between the two principal forms of endometrial carcinoma. Type I carcinomas, mainly characterized by endometrioid and mucinous types, are associated with hyperestrogenism, tend to affect younger women, and frequently show expression of estrogen and progesterone receptors. Their progression usually includes initial genetic occurrences like PTEN mutations, microsatellite instability (MIN), as well as K-ras and β-catenin mutations. Certain mutations, especially PTEN and K-ras, can already be found in atypical endometrial hyperplasia, which is the precursor lesion. In contrast, p53 mutations occur later and are observed in a minority of Type I cases. Type II carcinomas, such as serous and clear cell varieties, are not reliant on estrogen, typically occur in older females, and often do not express hormone receptors. These tumors frequently show p53 mutations, which can be identified even in precursor lesions such as endometrial intraepithelial carcinoma (EIC). Additional significant molecular alterations in Type II carcinomas are p16 inactivation, loss of E-cadherin, and amplification of her2/neu. The article highlights that these unique molecular pathways strongly advocate for reclassifying endometrial carcinomas beyond a strictly histological approach to a more biologically relevant, molecular-based classification, enhancing the comprehension of tumor behavior and informing treatment strategies [9]. CAR-T cell therapy represents a new and developing immunotherapeutic strategy for endometrial cancer (EC), especially in advanced or recurrent situations where conventional treatments are ineffective. The authors emphasize the rising occurrence and death rates linked to EC, particularly in those with metastatic conditions who face few treatment alternatives after standard chemotherapy. Despite the potential of immune checkpoint inhibitors such as pembrolizumab and dostarlimab for certain molecular subtypes of EC, including those with mismatch repair deficiency (dMMR) or high microsatellite instability (MSI-H), there remains a demand for more effective and lasting treatments. Adoptive cellular therapy (ACT), especially CAR-T cell therapy, has become a promising option. CAR-T cells are modified to identify tumor-associated antigens (TAAs), eliminating the requirement for antigen presentation through the major histocompatibility complex (MHC). This characteristic is especially beneficial in EC and various solid tumors where MHC expression is frequently diminished. The

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authors explain that CAR-T cells exhibit powerful antigen-binding and cytolytic functions, offering benefits compared to tumor-infiltrating lymphocytes (TILs) and T cell receptor-engineered cells (TCR-Ts), which are constrained by reduced survival in the immunosuppressive tumor microenvironment (TME) and complicated harvesting methods.The review additionally examines preclinical research, including studies focusing on the anti-Müllerian inhibiting substance type II receptor (MISIIR), which is highly expressed in various gynecological cancers. Findings from these studies indicate that MISIIR-specific CAR-T cells demonstrate antigen-specific functionality and the ability to eliminate tumor cells, pointing to a hopeful therapeutic avenue. The article also details the molecular architecture of CAR-T cells, consisting of various elements including an extracellular scFv domain for recognizing antigens, a transmembrane domain for stability, and intracellular signaling domains like CD3ζ, CD28, and CD137 that influence the functional generation and effectiveness of CAR-T cells[10]. Research on endometrial cancer has made considerable progress in early detection, therapy, and comprehension of risk factors. Endometrial cancer, a form of uterine cancer, mainly consists of two subtypes: endometrioid, the more prevalent type usually detected early, and non-endometrioid, which is rarer but more aggressive. While a standard screening test doesn't exist, researchers are investigating biomarkers and genetic risk factors to enable earlier diagnosis. Encouraging early detection initiatives consist of the DETECT Study, which utilizes samples collected from tampons to pinpoint biomarkers, and PapSEEK, a test that examines cells from the uterine lining for DNA alterations. Furthermore, women diagnosed with endometrial cancer are advised to undergo testing for Lynch syndrome, a hereditary condition associated with multiple cancers. Early-stage disease treatment generally consists of surgery, along with other possibilities like radiation, chemotherapy, hormone treatment, immunotherapy, and targeted therapies tailored to the specific disease characteristics. Progress in molecular profiling has resulted in recognizing four molecular subtypes of endometrial cancer, aiding in the customization of treatment strategies. Immunotherapy, particularly immune checkpoint inhibitors such as pembrolizumab and dostarlimab, has demonstrated effectiveness in managing tumors with mismatch repair deficiencies (dMMR) or high microsatellite instability (MSI-H), which can occur due to Lynch syndrome. These treatments are currently being utilized alongside chemotherapy and are undergoing new trials to broaden their application, even in individuals without dMMR. Targeted therapies, including combinations of cediranib and olaparib or drugs that target HER2, are being researched for the treatment of recurrent or advanced cases. Additional studies are investigating innovative combinations of surgery, chemotherapy, radiation, and targeted medications to enhance patient results. These research initiatives, backed by the National Cancer Institute (NCI), are fostering personalized and more efficient therapies for endometrial cancer, aiming to enhance survival rates and decrease disparities among various patient groups [11].A group of specialists carried out organized literature reviews and met online in January 2021 with stakeholders to examine the results. Uterine cancer, the most prevalent gynecological cancer in the U.S., is rising in both cases and death rates, especially among Black and Hispanic women and in high-risk types. The examination emphasized the difference between type 1 (low-grade, estrogen-reliant) and type 2 (aggressive, high-grade) endometrial cancers, with an increasing movement toward molecular classification for improved prognostic and therapeutic approaches. Considerable knowledge deficits persist, directing future research requirements [12].

TYPES OF UTERINE CANCER

Uterine cancer is one of the most common gynecological cancers generally classified into two main types based on histologic origin are endometrial carcinoma and uterine sarcomas. Endometrial carcinoma, which develops from the lining of the uterus, is the more common type and is further divided into two subtypes. Type I cancers are usually linked to estrogen, tend to be lower grade, and often have an endometrioid appearance whereas Type II cancers are not related to estrogen and are typically more aggressive, with serous or clear cell histology. On the other hand, uterine sarcomas are rare, aggressive tumors that arise from the muscle layer (myometrium) or connective tissue of the uterus. These comprises subtypes such as leiomyosarcoma, endometrial stromal sarcoma, and undifferentiated sarcoma.

Based on Histological Origin

A. Endometrial Carcinomas (Most common type – ~90%)

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• **Endometrioid adenocarcinoma**: Arises from the endometrial lining; estrogen-dependent; usually low-grade and slow-growing [13,15,16,21].
• **Serous carcinoma**: Aggressive, high-grade tumor; not estrogen-related; often presents in older women [13,16,21].
• **Squamous Cell Carcinoma**: very rare; arises from squamous cells of the uterus; often part of mixed tumors [13,15,16].
• **Neuroendocrine Tumors**: Rare tumors showing neuroendocrine differentiation (e.g., small cell carcinoma) [17].
• **Clear cell carcinoma**: Rare, high-grade tumor; aggressive; has clear cytoplasm [13,21].
• **Mixed carcinoma**: Contains more than one histological type (e.g., serous + endometrioid)[13].
• **Undifferentiated/dedifferentiated carcinoma**: Lacks distinct cell structure; very aggressive [13].
• **Carcinosarcoma (MMMT)**: Malignant mixed Müllerian tumor; has both carcinomatous and sarcomatous elements [19,22].

B. Uterine Sarcomas (Rare – ~3–7%)
• **Leiomyosarcoma**: Arises from uterine smooth muscle; highly aggressive and often recurs.[22]
• **Endometrial stromal sarcoma (ESS)**:
o **Low-grade ESS**: Slow-growing, hormone-sensitive.
o **High-grade ESS**: More aggressive and less hormone-sensitive.
• **Undifferentiated uterine sarcoma**: Poorly defined, very aggressive.
• **Adenosarcoma**: Mixed tumor of benign epithelial and malignant stromal components [22].

Based on Clinical and Hormonal Behavior
• **Type I (Estrogen-dependent)**:
o Includes endometrioid adenocarcinoma.
o Occurs in perimenopausal women.
o Associated with obesity, hyperestrogenism, and endometrial hyperplasia.
o Generally has a good prognosis [14,17,18,20,21].

• **Type II (Estrogen-independent)**:
o Includes serous, clear cell, and carcinosarcoma.
o Occurs in older, postmenopausal women.
o Not related to estrogen exposure.
o Poor prognosis, aggressive behavior [14,17, 18, 20, 21].

RISK FACTOR

Age- Age is a important factor in uterine cancer. It was shown that uterine cancer was more common in elderly women (60–64 years old) than in younger women (45–49 years old)[23].

Surgery- One of the biggest things that raises the risk of uterine cancer is surgery. In one study, two groups of women were contrasted. Women receiving hysterectomy for fibroids made up the first group, while women undergoing hysterectomy for genital prolapse made up the second. According to the findings, women in the first group had a 29% chance of developing uterine cancer, while those in the second group had a 0.1% probability[23].

Ethnicity- About 57.2% of non-Hispanic White women in a study involving 229,536 women had a higher risk of uterine cancer than non-Hispanic Black women (17.1%). This was because non-Hispanic Black women were regularly evaluated for uterine fibroids, which kept them aware of their condition [23].

Obesity (BMI ≥ 30)-A strong risk factor for endometrial cancer is obesity, accounting for 40% to 50% of all . It's associated with a 1.73x higher risk of uterine sarcoma [24].

History of diabetes: Women with obesity-associated diseases such as diabetes with a 2.33x higher risk [24].

Metabolic Factor-
To a lesser degree than obesity, metabolic syndrom e has also been linked to notable increases in risk[2 5].

Reproductive factors-Nulliparous women are at substantially higher risks than parous women, with infertility additionally contributing to risk .stfeeding has also recently emerged as a possible protective factor.Other established reproductive risk factors include young ages at menarche and/or old ages at menopause, potentially reflecting increased numbers of lifetime ovulatory cycles [25].

Menopausal hormone therapy- Especially long-term high-dose unopposed estrogen, increases endometrial cancer risk, while adding progestins particularly continuously helps reduce this risk[25].

Lifestyle factors-Cigarette smoking and moderate-to-active physical activity are independently associated with reduced endometrial cancer risk [25].

Familial and genetic factors-Family history of endometrial canceres pecially due to Lynch syndrome. It's significantly raises risk, though it accounts for only a small portion of cases; genetic studies have identified several common and

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rare variants modestly associated with risk, particularly for endometrioid cancers [25].

Tamoxifen use-Tamoxifen use in breast cancer patients increases endometrial cancer risk, especially soon after treatment, with high cumulative doses, and for aggressive tumor types[26,27].

Other factors-The impact of diet on endometrial cancer risk is unclear, though higher intake of fruits, vegetables, dairy, coffee, and green tea may reduce risk. High-fat diets and alcohol show no consistent link, while metformin and aspirin may slightly lower risk [25].

PATHOPHYSIOLOGY

PATHOPHYSIOLOGY OF TYPE I ENDOMETRIAL CANCER

Type I endometrial cancer, responsible for nearly 80% of endometrial cancers, is predominantly estrogen-dependent and is most often seen to arise in the setting of unopposed estrogen stimulation, for example, in obesity, anovulation, or estrogen replacement therapy [28].It tends to arise from endometrial hyperplasia, progressing to carcinoma by a well-established sequence [29]. At the molecular level, PTEN gene mutations are the most common early genetic changes, causing dysregulation of the PI3K/AKT signaling pathway, which enhances cellular growth and survival. [3]Other prevalent changes are microsatellite instability (MSI) and KRAS and β-catenin (CTNNB1) mutations [30,31].Type I tumors are characteristically endometrioid histologically, low-grade, and have a more favorable prognosis than Type II [29].The hormonal environment and genetic abnormalities together enhance endometrial gland growth, reduced apoptosis, and transformation to malignant change.

PATHOPHYSIOLOGY OF TYPE II ENDOMETRIAL CANCER

Type II endometrial carcinoma is a rare but more aggressive form of uterine cancer, estrogen-independent, and usually develops in an atrophic endometrium of postmenopausal women [28].It is not associated with unopposed estrogen exposure or endometrial hyperplasia. It usually presents with serous or clear cell histology, both of which are high-grade from onset [31].The mutation of TP53 is the primary molecular abnormality of serous carcinomas, which continue to show a high incidence of TP53 mutation (>90%) and thus thought to lead to abnormal function in TP53, which leads to genomic instability and inappropriate proliferation [30].Other alterations that are common include amplification of HER2/neu, mutations of PPP2R1A, and mutations of FBXW7 [5].These tumors have very high chromosomal instability, high rate of copy-number alterations, note TCGA [30].These clinically type II cancers invade the myometrium early and have rapid metastasis, therefore resulting in a poor prognosis [31].Overall, the aggressive nature of these tumors is due to dysfunctional p53 pathway, nad poor apoptosis and aberration of the cell cycle normal controls, regardless of the hormonal basis[31,32].

PATHOPHYSIOLOGY OF UTERINE SARCOMAS CANCER

Uterine sarcomas, are a rare and aggressive group of mesenchymal tumors, comprising 3–7% ofuterine malignancies, are those tumors which arise from the myometrial or connective tissue components of the uterus. These tumors have several subtypes, including leiomyosarcoma (LMS), endometrial stromal sarcoma (ESS), and undifferentiated uterine sarcoma (UUS) with unique molecular and histologic characteristics[33]. Leiomyosarcomas are the most prevalent subtype and typically have complex karyotypes, containing TP53, RB1, and ATRX mutations, causing uncontrolled proliferation with poor differentiation[34] .Low-grade endometrial stromal sarcomas often have JAZF1–SUZ12 gene fusions, which inhibit epigenetic regulation by changing polycomb repressive complexes[35].High-grade ESS, often associated with YWHAE–NUTM2A/B fusions, promotes aggressive growth[36].These tumors show high mitotic indices, necrosis, and erratic myometrial infiltration[33].Uterine sarcomas are generally hormone-independent, and pathogenesis is attributed to genomic instability or epigenetic regulation or disruption of cell cycle[34,35], such that uterine sarcomas can progress rapidly and metastasize very early[33].

TREATMENT OF UTERINE CANCER

1. Surgery is Usually the First Step

In utmost cases, treatment starts with surgery. Doctors generally remove the uterus, cervix, ovaries and fallopian tubes – a procedure called total hysterectomy with bilateral salpingo-oophorectomy. However , they may also check and remove near lymph bumps, if there is a threat the cancer has spread. This approach is extensively

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used and is considered the most effective starting point for early-stage endometrial cancer [37].

2. Radiation to Prevent Recurrence

Depending on the tumor's features like its size, grade, and how deeply it has invaded the uterine wall radiation therapy might be added after surgery. It helps reduce the risk of the cancer coming back. This could be brachytherapy (where radiation is placed inside the vagina) or external beam radiation directed at the pelvis.Clinical guidelines from European oncology groups support this as a way to prevent local recurrence, especially in higher-risk cases [38].

3. Chemotherapy for Advanced or Aggressive Cases

If the cancer has spread beyond the uterus or is more aggressive in nature, doctors will often recommend chemotherapy. The most commonly used drugs are carboplatin and paclitaxel, which are given through an IV. These medications have been shown to be effective in treating both advanced and recurrent endometrial cancers [39].

4. Hormonal Therapy – Especially for Younger Women

In cases where the tumor is hormone-sensitive and the cancer is low grade, hormonal therapy can be a good option especially for younger women who want to preserve fertility. This may involve oral progestins or a hormone-releasing IUD (like the levonorgestrel IUS). This approach is especially helpful for patients who can't undergo surgery or want to delay it [40].

5. Immunotherapy – A New Hope for Advanced Cases

Some cancers have specific genetic features that make them respond very well to immunotherapy. Drugs like pembrolizumab or dostarlimab have been approved for advanced or recurrent uterine cancer, particularly when tumors have mismatch repair deficiency (dMMR) or microsatellite instability (MSI-H). Studies have shown that combining immunotherapy with chemotherapy significantly improves survival in these cases [41,42].

6. Personalizing Treatment with Molecular Profiling

In recent times, there is been a big shift in how we classify and treat uterine cancer. Doctor now use molecular testing to check for mutations (like POLE, P53 or mismatch from issues). This helps determine which causes need redundant treatment and which can avoid gratuitous curatives. Guidelines now recommend testing as part of standard work-up for recently diagnosed cases [43,44].

7. After Treatment: Follow-up Care

After completing treatment, regular follow-ups are important to make sure the cancer hasn't come back. This usually includes a pelvic exam every few months, and sometimes scans if symptoms arise. The typical schedule is every 3–6 months for the first 2 years, then once or twice a year up to year five. These follow-up plans are based on NCCN guidelines and are adjusted according to the patient's risk level [45].

8. For younger women with early-stage, hormone-sensitive cancers who want to preserve fertility, doctors often use progestin therapy—either as oral tablets like medroxyprogesterone acetate or through a levonorgestrel-releasing intrauterine device (IUD). These approaches can sometimes control the cancer temporarily, allowing patients the chance to conceive before eventually proceeding to surgery if needed [46].

9. A breakthrough in recent years has been immunotherapy—particularly the combination of pembrolizumab (a PD-1 inhibitor) and lenvatinib (a tyrosine kinase inhibitor). This combination is now commonly used in patients with advanced or recurrent disease that isn't microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR) [47].

ADVERSE DRUG REACTION

Introduction to ADR (Adverse Drug Reactions)

Adverse Drug Reactions (ADRs) are negative or unintended effects caused by a medication that happen at standard therapeutic doses during clinical application. These responses can differ significantly in intensity—from mild issues like headaches or nausea to severe complications like liver failure, internal bleeding, or even death. ADRs pose a major issue in contemporary healthcare, as they can jeopardize patient safety, raise hospitalization rates, extend hospital stays, and hike overall treatment expenses. The analysis and oversight of ADRs are encompassed by pharmacovigilance, which is essential for the post-marketing monitoring of medications. Although clinical trials offer preliminary safety information, numerous ADRs

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only emerge after a drug is extensively utilized in the broader public. Thus, ongoing observation is crucial for recognizing emerging risks and guaranteeing the secure and efficient application of medications. Comprehending ADRs further aids in enhancing drug designs, advising healthcare providers in selecting safer options, and influencing regulatory measures like label alerts or market removal. In general, the prompt identification and appropriate handling of ADRs are vital measures in enhancing treatment results and protecting public health.

In an important 1975 review, Karch and Lasagna evaluated the definition, categorization, and clinical importance of adverse drug reactions (ADRs). The authors highlighted the absence of uniform criteria for detecting and documenting ADRs at that time, which frequently resulted in an undervaluation of their occurrence and intensity. They suggested a methodical strategy for differentiating between events caused by medication and those stemming from preexisting conditions or alternative treatments. The study also emphasized that ADRs significantly contributed to morbidity and mortality, frequently neglected in clinical decision-making. The authors urged for more stringent reporting mechanisms, heightened clinician awareness, and the combination of pharmacological and clinical information to enhance the identification and comprehension of ADRs. Their efforts established the foundation for contemporary pharmacovigilance practices. To sum up, the review highlighted that enhancing ADR identification and categorization is crucial for patient safety, improved treatment results, and well-informed regulatory guidelines [48] .The comprehension and handling of adverse drug reactions (ADRs) have progressed considerably over time, as shown in the studies by Karch and Lasagna (1975) and Al-Worafi (2020). Karch and Lasagna's thorough review highlighted the necessity for uniform definitions and approaches to accurately identify and document ADRs, pointing out that ambiguity frequently resulted in underrecognition and poor management. They emphasized that ADRs significantly contribute to patient suffering and death, urging for enhanced clinical awareness and pharmacological understanding. Expanding on this basic comprehension, Al-Worafi examined the difficulties of ADR monitoring in developing nations, emphasizing concerns like underreporting, fragile pharmacovigilance systems, inadequate healthcare infrastructure, and insufficient training for professionals. He highlighted the significance of education, policy enforcement, and global cooperation to improve drug safety. Both sources highlight that precise identification, efficient reporting, and robust pharmacovigilance systems are crucial for reducing ADR-related risks and safeguarding public health, particularly in resource-constrained environments [49]. Through years of investigation, the developing comprehension of adverse drug reactions (ADRs) highlights their significant influence on patient safety and public health. Karch and Lasagna (1975) established a foundation by highlighting the importance of precise definitions, uniform reporting, and clinical awareness, recognizing ADRs as a significant factor in morbidity and mortality frequently neglected in therapeutic choices. Expanding this viewpoint to resource-constrained environments, Al-Worafi (2020) examined how inadequate pharmacovigilance systems, insufficient professional training, and infrastructural deficiencies in developing nations worsen the underreporting and mishandling of ADRs. Recently, Jiang et al. (2022) performed an extensive retrospective study that highlighted the increasing issue of drug–drug interactions (DDIs) as a major factor in adverse drug reactions (ADRs). Their results showed a strong link between polypharmacy and significant ADRs, underscoring the need to incorporate DDI monitoring into pharmacovigilance frameworks. Collectively, these research findings show that although awareness of ADRs has increased over time, difficulties persist—particularly in real-world environments characterized by intricate drug therapies and inadequate infrastructure. Enhancing pharmacovigilance methods, encouraging education for healthcare providers, and utilizing data analytics are crucial for minimizing ADR-related hazards and improving patient-focused care [50].

The role of clinical pharmacists in reducing adverse drug reactions.

The existing research on adverse drug reactions (ADRs) consistently emphasizes their significant impact on patient safety, treatment results, and healthcare systems. Karch and Lasagna (1975) delivered one of the first thorough examinations of ADRs, highlighting the absence of standardized definitions and reporting methods that impeded precise identification and handling. Years later, Al-Worafi (2020) concentrated on the specific obstacles encountered in developing

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nations, including underreporting, lack of training, and weak pharmacovigilance systems, which all lead to delayed identification and ineffective management of ADRs. Expanding on this, Jiang et al. (2022) demonstrated that drug–drug interactions (DDIs), especially in scenarios of polypharmacy, represent a major and preventable source of ADRs, highlighting the necessity for improved monitoring tools and data-informed screening techniques. Supporting these findings, Alqurbi and Atiah (2020) showed the vital function of clinical pharmacists in reducing ADRs via proactive patient monitoring, medication assessment, and teamwork across disciplines. Collectively, these studies emphasize the importance of a strong, comprehensive strategy for ADR prevention—incorporating standardized reporting systems, enhanced healthcare infrastructure in developing countries, DDI monitoring, and the inclusion of clinical pharmacy services. Ultimately, enhancing ADR management necessitates collaborative actions across healthcare systems to promote safer medication usage and improve patient outcomes [51].

ADR IN UTERINE CANCER MEDICATION

In the experimental research, Yu et al. (2014) investigated the combined effects of sodium butyrate on the toxicology of adriamycin (doxorubicin) in human uterine cancer cells. The study revealed that sodium butyrate markedly increased adriamycin-induced cell death by facilitating apoptosis via the downregulation of human telomerase reverse transcriptase (hTERT). As hTERT is essential for cellular immortalization and cancer advancement, its inhibition resulted in heightened sensitivity of cancer cells to chemotherapy stress. The joint treatment resulted in increased amounts of apoptotic markers than either treatment alone, suggesting a possible therapeutic benefit. The research concludes that sodium butyrate may serve as a beneficial adjuvant in uterine cancer treatment by enhancing the effectiveness of standard chemotherapy via hTERT-targeted apoptotic mechanisms [52].Pectasides et al. (2007) conducted a thorough review of systemic therapies employed in the treatment of metastatic or recurrent endometrial cancer, emphasizing chemotherapy, hormonal therapy, and new targeted therapies. The research emphasized that although endometrial cancer is typically identified early and effectively managed through surgery, recurrent or metastatic instances pose considerable treatment difficulties. Chemotherapy protocols, especially combinations such as paclitaxel, doxorubicin, and cisplatin (TAP), demonstrated moderate effectiveness but had significant toxicity. Hormonal treatments like progestins and tamoxifen proved advantageous in certain hormone-receptor-positive instances with reduced tumor burden. The review also addressed initial trials of targeted therapies, although they had little success at that time. The authors determined that although systemic therapy provides palliative advantages, its efficacy is still restricted, highlighting the necessity for personalized treatment approaches and additional exploration into more effective and less harmful therapeutic options for advanced endometrial cancer [53]. Scambia et al. (1992) studied the antitumor properties of quercetin, a flavonoid from plants, on primary ovarian and endometrial cancer cells, as well as its interactions with cis-diamminedichloroplatinum (II) (often referred to as cisplatin). The research showed that quercetin notably hampered the growth of ovarian and endometrial cancer cells in vitro by causing cell cycle arrest and decreasing DNA synthesis. Importantly, when combined with cisplatin, quercetin showed a synergistic effect, boosting cisplatin's cytotoxicity while not raising toxicity to normal cells. The findings indicate that quercetin possesses not only independent anticancer properties but also enhances the effectiveness of standard chemotherapy. The authors determined that quercetin could act as a beneficial supplement in gynecologic cancer treatment, advocating for additional investigation into its mechanisms and clinical usage, especially in improving results of platinum-based therapy in endometrial cancer [54].

ADR IN ENDOMETRIAL CANCER MEDICATION

In PhD dissertation, Santana (2020) performed a retrospective study to investigate treatment trends, surgical delays, and compliance with National Comprehensive Cancer Network (NCCN) guidelines in Puerto Rican women diagnosed with endometrial cancer from 2009 to 2015. The research indicated that a significant portion of patients faced delays in undergoing surgery and did not receive treatment that fully adhered to established NCCN guidelines. These variances were strongly linked to worse clinical results, particularly in cases identified at a later stage. Elements contributing to these disparities comprised systemic inefficiencies, restricted healthcare access, and institutional limitations.

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Santana determined that prompt surgical action and rigorous compliance with clinical protocols are essential for enhancing survival rates and overall results. The results highlight the necessity for healthcare reforms in Puerto Rico to minimize treatment delays and encourage adherence to guidelines, ultimately seeking to guarantee equity and efficacy in cancer management [55]. Halla (2022) examines recent developments in treating advanced or recurrent endometrial cancer, emphasizing new systemic therapies that extend beyond conventional chemotherapy. The article emphasizes the increasing significance of immune checkpoint inhibitors (like pembrolizumab) and targeted treatments, especially for tumors characterized by distinct molecular traits such as microsatellite instability-high (MSI-H) or mismatch repair deficiency (dMMR). Combination therapies, like pembrolizumab paired with lenvatinib, have demonstrated encouraging outcomes in enhancing progression-free survival and response rates in previously treated patients. The article highlights the transition to personalized medicine, wherein tumormolecular profiling informs treatment choices, improving effectiveness while reducing unwarranted toxicity. Halla concludes that these innovative therapies are transforming the treatment landscape of endometrial cancer, providing renewed hope for patients with few options and emphasizing the necessity of ongoing clinical trials and biomarker-driven strategies [56]. Fortuny et al. (2009) performed a case–control study to assess the impact of specific medical conditions and medication consumption on the likelihood of developing endometrial cancer. The research revealed that women with prior obesity, diabetes, and hypertension had a notably higher risk, reinforcing the influence of metabolic and hormonal elements in the development of endometrial cancer. The study also discovered that estrogen-only hormone therapy increased the risk of cancer, whereas combined estrogen–progestin therapy seemed to have a more neutral impact. Notably, the research examined links with medications like nonsteroidal anti-inflammatory drugs (NSAIDs) and oral contraceptives, observing certain protective patterns, although the findings were not consistently significant. The authors determined that both existing health issues and medication exposures significantly influence the risk of endometrial cancer, highlighting the necessity of thorough patient histories and risk-factor evaluations in prevention and early detection efforts [57].

ADR IN UTERINE SARCOMA MEDICATION

Gadducci et al. (2008) provided an extensive analysis of the management challenges associated with uterine sarcomas, a rare and aggressive category of uterine cancers. The article describes the clinical and pathological diversity of uterine sarcomas, such as leiomyosarcoma, endometrial stromal sarcoma, and undifferentiated uterine sarcoma, all exhibiting unique behaviors and responses to treatment. The writers highlighted that surgical excision, mainly total hysterectomy, continues to be the fundamental treatment, while the benefits of adjuvant chemotherapy and radiotherapy are still contested because of insufficient and unclear evidence. They observed low overall survival rates, particularly in later stages, along with a significant recurrence rate even following complete removal. The evaluation additionally addressed new treatments and the necessity for more solid, forward-looking clinical studies. In summary, the authors characterized the management of uterine sarcoma as an ongoing clinical difficulty that necessitates tailored treatment strategies, teamwork among various specialties, and enhanced research initiatives to support evidence-informed choices and enhance patient results [58].Benson and Miah (2017) offered a refreshed clinical viewpoint on uterine sarcomas, highlighting their infrequency, biological variation, and difficult treatment scenario. The article examined the main subtypes—leiomyosarcoma, endometrial stromal sarcoma, and undifferentiated uterine sarcoma—each varying considerably in outlook and treatment reaction. Surgery, especially total hysterectomy, continues to be the primary treatment; however, the effectiveness of adjuvant therapy (radiation and chemotherapy) is uncertain because of insufficient solid evidence backing survival advantages. The writers emphasized the latest progress in molecular profiling and targeted treatments, providing optimism for improved patient classification and upcoming therapeutic possibilities. Even with these advancements, recurrence rates continue to be elevated and the overall outlook is bleak, particularly in high-grade sarcomas. The authors determined that further research is critically necessary, and that the treatment of uterine sarcoma should preferably take place in specialized centers equipped with multidisciplinary

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teams and clinical trials to enhance long-term results [59].Lin et al. (2015) investigated the molecular mechanisms that contribute to doxorubicin resistance in uterine sarcoma, emphasizing the importance of progesterone receptor membrane component 1 (PGRMC1). Utilizing the MES-SA uterine sarcoma cell line, the research showed that increased PGRMC1 expression plays a crucial role in chemoresistance by enhancing cell survival, decreasing apoptosis, and stimulating essential survival pathways like PI3K/AKT. The researchers demonstrated that silencing or inhibiting PGRMC1 made the cancer cells more responsive to doxorubicin, enhancing drug-induced cytotoxicity. These results indicate that PGRMC1 acts as a crucial mediator of drug resistance and may represent a possible therapeutic target to improve the effectiveness of chemotherapy in uterine sarcoma. The research indicates that focusing on PGRMC1 could enhance treatment results in individuals with chemoresistantuterine sarcomas, opening avenues for innovative combination therapies [60].

INTERPRETATION OF ADR IN UTERINE CANCER MEDICATION.

The body of studies covering different aspects of uterine and endometrial cancer highlights the intricacies of its treatment, biological foundations, risk elements, and advancements in therapy. Santana (2020) emphasized the negative effects of postponed surgery and non-compliance with NCCN guidelines among Puerto Rican women with endometrial cancer, connecting systemic disparities to unfavorable outcomes. Fortuny et al. (2009) additionally highlighted the influence of comorbidities like obesity, diabetes, and hypertension and specific medications on elevating endometrial cancer risk, underscoring the importance of thorough patient profiling in prevention and early intervention efforts. In the therapeutic realm, Pectasides et al. (2007) examined systemic treatments for advanced/recurrent endometrial cancer, noting the low effectiveness and significant toxicity of conventional chemotherapy protocols, whereas Halla (2022) highlighted the encouraging rise of immunotherapy and targeted therapies, especially in biomarker-oriented scenarios. Yu et al. (2014) and Scambia et al. (1992) investigated cellular-level treatment improvements, demonstrating that sodium butyrate and quercetin, respectively, increase the effectiveness of chemotherapeutics such as doxorubicin and cisplatin by facilitating apoptosis in endometrial cancer cells. Concerning uterine sarcomas, Gadducci et al. (2008) and Benson & Miah (2017) emphasized the tumors' aggressive characteristics and unfavorable prognosis, mentioning the absence of definitive guidelines for adjuvant treatment and the significance of coordinated, multidisciplinary care. Molecular findings by Lin et al. (2015) indicated that the overexpression of PGRMC1 plays a role in doxorubicin resistance in uterine sarcoma, suggesting a possible target to address chemoresistance. Together, these studies demonstrate the complex factors involved in uterine cancers, where timely diagnosis, precise medicine, molecular targeting, and healthcare equity align as essential foundations for enhancing patient outcomes

FUTURE PROSPECTIVES OF UTERUS CANCER

Significant advances in our understanding of the genesis of Uterus cancer and the changing demographics of those diagnosed with the disease have led to radical changes in the diagnosis and treatment of this disease. For the first time, these advancements have also made possible disease prevention strategies visible. The increasing personalization of therapy based on patient and tumor characteristics is at the heart of these advancements. This means that women are starting to receive tailored treatments meant to optimize oncological benefits while reducing the likelihood of adverse side effects. This trend is anticipated to continue as we gain a better understanding of the ways in which genetic and environmental factors combine to cause endometrial cancer [61].

Our knowledge of endometrial cancer biology has grown over the past few decades, primarily as a result of the development of molecular techniques applied to the various preclinical models that are currently available.

Future preclinical and clinical research was made possible by the use of both in vitro and in vivo models, which helped to clarify many facets of the illness. Since a model is by definition imperfect in simulating a genuine situation, and it naturally has actual advantages for one element but downsides for another. As a result, the scientific community is becoming more interested in the concept of using integrative preclinical platforms with many models for a single cancer type. the use of various methods and models to take advantage of efficient precision medicine platforms [62].

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Chimeric antigen receptor (CAR)-T cell immunotherapy is being used more and more to treat solid tumors. This therapy platform enables T cells to generate tumor-specific CARs on their cell surface, which can then be administered to the patient to treat neoplastic cells. Even though CAR-T cell therapy has shown promise and clinical benefit when compared to other T cell treatment platforms, more research is required to overcome physiological limitations such as CAR-T cell depletion, immunosuppressive tumor microenvironment, and the lack of specific target molecules. The current use of CAR-T cell therapy for endometrial cancers is examined in this review. We also discuss the serious side effects and limitations of this immunotherapeutic approach. Last but not least, we incorporate advancements and early-stage clinical trials that are signal-seeking and have produced positive results, leading to the approval of new immunotherapeutic medications for the disease [64].

II. CONCLUSION

Uterine cancer, mainly endometrial cancer, is a major health concern for women due to its increasing prevalence, especially in high-income nations and among younger women. Although many cases are diagnosed early due to the warning sign of abnormal uterine bleeding, many cases are discovered at advanced stages, particularly in underprivileged communities with limited access to timely medical care.

More knowledge about the genetic and molecular causes of uterine cancers has emerged in recent years. The development of molecular classification systems, like the Cancer Genome Atlas (TCGA) classification, has completely changed how doctors determine prognosis and customize treatment regimens. Additionally, thanks to novel treatments like immune checkpoint inhibitors and personalized medicine, the range of available treatments has increased beyond conventional surgery and chemotherapy.

As we look ahead, the incorporation of artificial intelligence in diagnostic imaging, the application of liquid biopsies for tracking recurrence, and the investigation of innovative agents like antibody-drug conjugates and EZH2 inhibitors are expected to significantly improve early detection and treatment effectiveness. Public health initiatives should now not only concentrate on treatment but also on preventative measures, such as tackling obesity, diabetes, and hormonal risk factors that are known to contribute to uterine cancer.

In the end, addressing uterine cancer necessitates a collaborative approach that merges advanced research, enhanced clinical care, and increased public awareness. By prioritizing prevention, timely diagnosis, tailored therapies, and healthcare equity, we can alleviate the impact of this disease and strive for enhanced outcomes and healthier, longer lives for women worldwide.

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