Pathophysiology Of Breast Cancer

The Pathophysiology of Hormone Receptor-Positive Invasive Ductal Carcinoma & Molecular-Basis Behind Therapy

Breast cancer is the most prevalent form of cancer in females. There were 1.67 million cases reported worldwide in 201212.

SECTION A -

The patient is diagnosed with invasive ductal carcinoma (IDC) which is considered rampant of all cancers. This form of cancer begins in the cells which line the milk ducts or lobules of the breast and infiltrate into the surrounding tissue1. Generally, cancer can be the result of DNA changes or mutations that can be inherited, which increases the risk of development5. However, DNA mutations linked to breast cancer are predominantly acquired2; this is significant for the patient as she has no previous medical history of breast cancer. Mutations in DNA can consequent in the mutations of genes and potentially alter the balance between controlled cell growth and death as normal function is distorted2. Risk also increases with elderly (e.g. post-menopausal) women, especially in individuals who experience a later onset of menopause5. This patient's case of IDC is acknowledged as hormone receptor-positive following immunocytochemical methods that observed the tumor mass as both estrogen receptor (ER)-positive and progesterone receptor (PR)-positive I.e. the cancer cells are growing in response to estrogen and progesterone steroid hormones.

Oestrogen is a steroid hormone that facilitates the growth, reproduction, and development of many mammalian tissues. It can be synthesized in extragonadal organs and tissues such as the mesenchymal cells of adipose tissue in the breasts, and its physiological actions moderated by its corresponding receptors, ER? and ER?3. These receptors are ligand-activated transcription factors that act by binding to DNA in the nucleus of cells10, both receptors uniquely contribute to carcinogenesis and tumor progression7. ER? (encoded by ESR1 gene located on chromosome 6q2510) is a key endocrine regulatory protein in ER-positive breast cancer, thus a primary indicator of endocrine responsiveness. Its structure is composed of a DNA-binding domain, an N-terminal AF1 domain, and a C-terminal ligand-binding region9. Oestrogen has high affinity and specificity for ER? where binding can activate a genomic pathway that initiates coregulator growth factors and G-protein coupled signalling4. The hormone is pivotal in cell cycle progression as it binds with cyclin-dependent kinase 4/6 (CDK4/6) to facilitate the G1 to S phase transition through cyclin D1 (CD1) activation. Dysregulation of this pathway is associated with tumorigenesis e.g. overexpression of CD14. Naturally, ER? is localized in the cytosol of cells where steroid hormone estrogen can passively diffuse through the cell membrane and bind specifically to the receptor. Post-binding, the complex can translocate into the nucleus and interact with the C-terminal ligand-binding domain of the receptor to induce a conformational change that initiates gene transcription10,11. RNA-polymerase and specific cofactors are recruited which bind to ER at the promoter through estrogen-response elements (ERE),

enabling RNA-polymerase to generate a copy strand of the target genes. This mRNA strand is then exported from the nucleus to nearby ribosomes where it can be translated to proteins. Estrogen receptor promoter B associated factor 1 (ERBF-1) is critical for the transcription activity of promoter B in ER?-positive breast cancer cells; it is exclusively expressed in cells expressing ER? mRNA transcribed from promoter B and plays an important role in the expression of the ER? gene in breast cancer.

Progesterone receptors are also ligand-activated transcription factors. It is a vital regulator of transcription and in initiating signal transduction pathways that are connected to proliferative signaling in breast cancer. PR-A and PR-B are the two prevalent isoforms of PR, made from the same gene but with differing translation sites29. Isoforms are typically expressed in response to ER?-mediated transcriptional events30; therefore, it is not surprising that the patient is both ER-positive and PR-positive. PR-B is significant in PR-positive cases as it acts in normal mammary gland development and has been expressed in proliferating cells. Post-binding with progesterone, the receptor experiences a conformational change and translocates into the nucleus where it can interact with coregulator molecules through progesterone-response elements (PRE)31. The receptors act with mitogenic protein kinases and cell-cycle mediators (e.g. CDK2, cyclins A, and E) to elicit regulation of target genes and proliferative responses.

SECTION B -

Aforementioned, the patient is diagnosed with hormone receptor-positive as her tumor mass expressed both ER and PR. Hormone receptor-positive oncology cases are prevalent in older women in comparison to young1, this diagnosis is notable for the patient as she is 63 years of age. Fortunately, HR-positive cancer patients generally have promising responses to treatment with hormone therapy drugs6,8, which can act to either block or lower abnormal levels of hormones within the body. Inhibition of steroid hormone attachment to their specific receptors on breast cancer cells can prevent further growth and spread of the cancer1.

Selective estrogen receptor modulators (SERM) including Tamoxifen, are drugs that block ERs on breast cancer cells. They are effective therapy for ER-positive breast cancer owing to their ability to imitate estrogen and interact with the ligand-binding domain of ERs to induce changes that prevent gene expression regulation8. Mimicking of estrogen by SERMs is achieved due to the similarities in their structures [INSERT FIGURE]. When prescribed during the early stages of cancer, Tamoxifen can decrease the rate of recurrence in ER-positive patients13. However, a limitation to the frequent use of Tamoxifen is developed endocrine resistance that renders the modulator ineffective, this can give rise to further tumor growth and metastasis to other organs. Furthermore, treatment is exclusively for pre-menopausal women; Toremifene is an alternative drug that is typically prescribed to treat metastatic carcinoma in postmenopausal women. The serious side effects of SERMs therapy in postmenopausal women can be an increased risk of attaining strokes and developing uterine cancer, which is indicated early by abnormal vaginal bleeding.

Fulvestrant is an anti-oestrogenic drug that blocks and damages ER proteins I.e. selective estrogen receptor degraders (SERD). Similar to SERMs, the drug binds to the ligand-binding domain of ERs with an affinity like oestrogen4, however, elicits degradation of the receptor complex; SERDs competitively inhibit the binding of estrogen hormones to their receptor. ER degradation is achieved through inhibition of receptor dimerization, transcription inactivation,

and accelerated receptor downregulation. It can be prescribed in combination with a CDK4/6 inhibitor to treat metastatic breast cancer, which is only provided for postmenopausal women. During the cell cycle, fulvestrant increases the percentage of cells in the G0/G1 phase, thus reducing the amount of DNA synthesized. The short-term side effects of the drug include headaches, bone pain, mild nausea, and hot flashes.

Aromatase is a rate-limiting enzyme that facilitates estrogen production in post-menopausal women. Aromatase inhibitors (AI) function by blocking this process within the tumor microenvironment and tumor progression are interrupted due to estrogen ligand deficiency. Thus, AIs (e.g. Exemestane irreversible and letrozole reversible) are most frequently advised and effective in treating postmenopausal women14,15. Prescription of AIs following tamoxifen (switch strategy) medication has also been known to induce considerable reductions of recurrence13,14. There are two categories of AIs determined by their molecular structure; steroidal (Type I) and non-steroidal (Type II). Exemestane is an example of a steroidal AI that elicits permanent inactivation and degradation of the enzyme through competitive binding with aromatase; letrozole is a nonsteroidal AI that inhibits the conversion of androgens to estrogens. The side effects that are caused by AIs are typically the result of estrogen deprivation, including myalgia or arthralgia and musculoskeletal disorders e.g. osteoporosis15.

Selective progesterone receptor modulators (SPRM)

The patient is considered HER2-negative meaning that the cancer cells don’t contain high levels of human epidermal growth factor receptor 2 (HER2) protein. Patients diagnosed with HER-negative are more likely to respond to breast cancer chemotherapy.

SECTION C -

The ability of an organism to develop newer characteristics increases its virulence, which allows it to colonize different areas within the host and evoke infection. Some enterococcal species (e.g. E. faecalis and E. faecium) naturally inhabit the gastrointestinal tract as part of the normal human flora16-18 but can become opportunistic in immunocompromised individuals; virulence factors play an important role in this. Infection risk increases with patients that are on antibiotic medication as a result of a disturbed intestinal microbiota20, this is consequential for the patient’s case as she suffered from recurrent bladder infections following lumpectomy and chemotherapy. E. faecalis causes the majority of enterococcal infections overall with several that are nosocomial conditions26. The conditions caused by enterococci are endocarditis, septicemia, bacteremia, and urinary tract infections (UTI)18,22. Several significant virulence factors have been recognized in enterococcal spp. which are associated with its pathogenicities such as gelatinase, an aggregation substance, capsule, enterococcal surface proteins (ESP), and biofilms16,17. The genes that encode these factors are situated on Pathogenicity Islands which are specific regions of the genome prevalent in outbreak strains of vancomycin-resistant enterococci (VRE). In high cell density populations, gene expression regulation is achieved through quorum sensing21. Gelatinase is a protease that hydrolyses gelatine, collagen, hemoglobin, and other peptides. Along with surface proteins, it has been connected to biofilm formation, which is strongest in UTIs compared to blood isolates; biofilms and their hydrophobicity are pivotal in bacterial pathogenesis21. Enterococcal surface proteins (ESP) encoded by esp are associated with bacterial cell walls and are primary agents in urinary tract infection (UTI) colonization via adherence to the bladder epithelium with assistance from

aggregation substances and collagen-binding proteins; adherence is essential for inducing infection within the host18-21.

Enterococcal species are intrinsically resistant to several antimicrobial agents (e.g. vancomycin and ciprofloxacin), biofilms play a pivotal role in achieving this22; biofilms are accumulations of microorganisms irreversibly attached to one another known to promote resistance to environmental stress and adhesion to eukaryotic cells23 e.g. urinary tract. The proximity of microorganisms in this structure encourages resistance genes transfer between communities, thus enabling them to develop resistance from antimicrobials. Furthermore, the structure limits the concentrations of antibiotic diffusion through the matrix, and even after penetration antibiotics can be inactivated by the change in metal ion and pH concentration inside the biofilm23,24. Biofilms are also capable of expressing efflux pumps.

E. faecalis is a common cause of UTIs in adult women and is generally asymptomatic24,25. Postmenopausal women are more at risk of developing UTIs due to decreased estrogen production, which is necessary in maintaining healthy vaginal fluid acidity that acts to protect against pathogenic organisms24. The patient will likely have acquired this bladder infection from the hospital during their chemotherapy sessions as it causes immunosuppression.

The primary mechanism of glycopeptide resistance (e.g. vancomycin/VRE) in enterococci involves the alteration of the peptidoglycan synthesis pathway, specifically the substitution of normal peptidoglycan precursors D-Alanine-D-Alanine to either D-Alanine-D-Lactate or D-Serine26. This alteration resulted in variable expressions of glycopeptide resistance e.g. reduced the binding affinity of glycopeptide drugs to .001 times26. = gene transfer in biofilms. Vancomycin is a cell wall-active drug26, therefore changes in cell wall composition inhibited the drug’s effects.

Ciprofloxacin is a bactericidal antibiotic and the most potent of the fluoroquinolone drug class against gram-negative bacilli bacteria27. It acts by stopping DNA replication by inhibiting bacterial DNA topoisomerase II and DNA-gyrase which are vital for bacterial cell division/transcription, therefore the drug prevents replication28. In vitro resistance is commonly the result of mutations in bacterial topoisomerases and DNA-gyrase through multi-step mutations, whereas single mutations may cause susceptibility