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Insight into Inflammatory Breast Cancer

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Accurate statistics for the misdiagnosis or misclassification of unusual cancers are not readily available in the literature, however anecdotal evidence from advocacy and support groups abounds. This is particularly true for inflammatory breast cancer (IBC). IBC is considered one of the most aggressive and invasive of breast cancers. The overall survival rate for IBC patients is 40% for 5 years and 20% for 10 years compared to 87% for all breast cancers. Unfortunately, the incidence of IBC has been steadily increasing over the past decade, with more women presenting with the disease, being misdiagnosed, receiving inappropriate treatment and dying.

IBC has a unique presentation, occurring in young women and even girls as young as 12 years old. IBC is distinct from other forms of breast cancer both phenotypically and molecularly. A conspicuous mass is often lacking in IBC, rather the tumor presents as sheets or cords within the breast. The tumor invades the dermal lymphatic vessels of the skin overlaying the breast, forming tumor emboli and disseminates throughout the body. The skin overlying the breast appears inflamed, is thickened and often has a red or purple coloration; however no immune effector cell infiltrate is present. The breast is usually tender and sore. The onset of symptoms is extremely rapid and the cancer can progress to metastatic disease within 6 months of the onset of symptoms. Literally patients have described going to bed with no symptoms and then waking up with a swollen, warm and painful breast.

IBC accounts for up to ~11,000 of total breast cancer cases in the United States, however over 90% of women with IBC are initially evaluated by a primary care or gynecological physician and empirically treated with antibiotics with the presumed diagnosis of mastitis. Subsequently, after a variable period of time from this initial evaluation, the women are eventually referred for imaging and other diagnostic breast evaluations to confirm the diagnosis of "breast malignancies" that are frequently not referred to as IBC. Deaths from unclassified IBC are not counted in NCI Surveillance, Epidemiology and End Results (SEER) data, which lead to an under reported numbers of cases. This lack of reporting also results in a classification of "rare" breast cancer, which has the effect of discounting the symptoms a delaying diagnosis and treatment. Because of misdiagnosis and delay in treatment, many women rapidly lose their battle with IBC.

Current therapies based on surgery or radiation would target initial dissemination sites, the breast itself, axial lymph nodes and the chest wall. Chemotherapy, while targeting distant dissemination, has proven ineffective and cannot be sustained at high enough levels for long enough periods without encountering toxicity. Therefore only a limited number of treatment options exist, none of them very successful. Multiple epidemiological studies link an inverse relation between Vitamin D_3 and breast cancer risk, current randomized clinical trial results have not confirmed this link. The discrepancy is due to the variable and insufficient dosage of calcitriol used in the trials. For example, a randomized double blind seven year study revealed no correlation between breast cancer risk and Vitamin D_3 supplementation. The dose of Vitamin D_3 given in this study was 400 IU/day, far below the required 1700 – 2000 IU needed to produce a 25(OH)D_3 serum level of 75 nmol/L which had been linked to low breast cancer risk. The dose of calcitriol used is crucial not only in a preventative application but especially in a therapeutic application. Current experiments *in vitro* and *in vivo* in mice suggest that high levels of calcitriol may reduce tumor migration invasion and emboli size of IBC. However the problem maybe the delivery of calcitriol to the tumor and metastasis site specifically. Since calcitriol plays a central role during many cellular processes and also modulates immune responses high doses of calcitriol may induce adverse side effects. Well known side effects are hyperglycemia.

Additionally, calcitriols role in T cells, macrophages and dentritic cell maturation are well established. Its association with inflammatory diseases is now also well documented. Since patients with IBC may need to stay on calcitirol for long time periods, the safety of long term calcitriol administration must be examined or a more targeted approach for the delivery of clacitriol to tumor sites must be developed.

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