The role of aromatase inhibitors in slim women with 'breast cancer related lymphoedema': a reflective case series

Clare Anvar
MLD/Clinical Massage Specialist; Clinical Therapy Advisor at Lipoedema UK
clareanvar@hotmail.co.uk

Delivering the best, evidence-based care is dependent on using reflective processes to improve outcomes. Protocols for breast cancer patients are constantly evolving, with more complex surgeries, new drugs and treatment regimens. Lymphoedema patients often present with challenging, multifaceted co-morbidities to unpick, before successful management plans can deliver results.

From January 2023 and over a 3-month period, five slim, White women were referred by breast care nurses. They presented with similar, unusual 'breast cancer-related lymphoedemas', which were not responsive to standard, conservative treatment. When the fifth woman presented, cases were collated and the literature was reviewed, which led to a renewed understanding of their symptoms and referrals back to their consultants.

Abstract

Background: This case series follows the reflective processes undertaken, when 5, slim women presented with reactive oedemas of the forearm and hand, that did not respond to usual therapy. **Aim**: To raise awareness about Aromatase Inhibitor (AI), Letrozole. **Methods**: Possible causes, Cycline-Dependent Kinase 4 and 6 (CDK4/6) inhibitor, Ribociclib and Axillary Web Syndrome were explored and reviewed, as effective treatment options were sought. New cases presented, which discounted each theory, until Letrozole was suspected. **Results**: Inflammatory oedemas were explained by the mechanisms-of-action relating to Aromatase Inhibitor Associated Musculoskeletal Syndrome (AIMSS), the severity of which, especially for slim women with oestrogen deprivation, causes almost 50% of women to cease treatment within 6 months; risking disease reoccurrence. **Conclusion**: Permissions were gained, a table was collated and sent to referring consultants, requesting risk/benefit analysis of Letrozole with a medication review. If non-responsive, inflammatory oedemas present in clinic, AIs should be considered as a trigger.

Keywords: Aromatase inhibitors • Aromatase Inhibitor Associated Musculoskeletal syndrome • letrozole side effects • oestrogen deprivation • Aromatic Inihibitors with CKD4/6 inhibitors

Case studies

Case one

Referred from hospital one, the patient was a 62-year-old woman, with a body mass index (BMI) of 22 and stage 4 Oestrogen Receptor positive (ER+) breast cancer with bone metastases. She had undergone a mastectomy 4 months prior, along with an implant reconstruction with a titanium sling. Of the 17 lymph nodes removed, 16 were positive. Prior hysterectomy and oophorectomies were recorded. She had received radiotherapy and had Axillary Web Syndrome (AWS) with four cords, which had been resolved through physiotherapy. No existing co-morbidities were noted, and was considered fit and very active. Medication included Ribociclib and Letrozole (Denosumab ceased due to side effects).

However, there was a sudden onset two weeks prior to referral, with the forearm, hand, thumb, index and middle finger showing oedema with pain in the wrist.

Manual lymphatic drainage (MLD) was performed. Separate, Class 2 compression glove and sleeve were chosen, due to the specific pattern of swelling in the fingers/hand and level of activity. The patient immediately reacted with inflammation, redness and balloon swelling of her hand. Was the overlap of garments at the wrist constricting? Were they poorly measured? Was Class 2 not appropriate? Her arm was small and shapely. A top band was specifically omitted on the sleeve, so as not to constrict the arm and impair drainage. Class 1 garments were provided but the same reactions occurred.

Case two

A 47-year-old woman was referred from hospital one, with a BMI of 24 and stage 3, ER+ breast cancer with bone metastases and a latissimus dorsi flap reconstruction, which occured 12 months prior. She also had a full axillary clearance prior to hysterectomy. She was fit with a young family. She underwent radiotherapy and had mild, unresolved AWS. Medications included Ribociclib, Letrozole and Zoladex. Sudden onset oedema of the forearm, hand, thumb, index

and middle finger, were noted.

MLD was performed accordingly. Class 2, sleeve and glove were provided. However, an immediate inflammatory reaction was experienced. This was changed to Class 1 and a larger size, but this too resulted in the same reaction.

Ribociclib

Both women were taking Ribociclib with Letrozole. Could this have caused inflammatory oedema? Of the 2 million women diagnosed with breast cancer each year, 75% of tumours are ER+. At the time of diagnosis, localised disease represents around 64%, while 6% have developed metastases. The 5-year survival rate from metastatic disease is estimated at 27% (Skafida et al, 2023). The use of third generation aromatase inhibitors (AIs), Letrozole, Anastrozole (non-steroidal) and Exemestane (steroidal) is standard; yet, endocrine resistance and disease progression still occurs in approximately 50% of these patients (Presti and Quaquarini, 2019). Ribociclib is one of three drugs (Ribociclib, Palbociclib and Abemaciclib) known as Cyclin-Dependant Kinases 4/6 inhibitors (Scott et al, 2017). They block the action of an abnormal protein that signals cancer cells to multiply and interact with the aromatase pathway, reducing disease progression and resistance to AIs (Ding et al, 2020). Phase 111 studies showed that a synergy of CDK4/6 inhibitors with non-steroidal AIs improved progression-free survival by 40–45% and lowered the risk of death by 24% at 80 months (Murphy and Dickler, 2015). However, while they carry a high risk of neutropenia and hepatobiliary toxicity (Finnsdottir et al, 2021; Watt and Goel, 2022), they have not been linked to musculoskeletal symptoms (Skafida, 2023).

Soon after, Ribociclib was discontinued for Case one, following the second, 28–day cycle, due to skin reactions, and liver enzymes that were four times more elevated, indicating liver toxicity and very low lymphocytes.

Overnight, cotton, ribbed, combined sleeve/mitten compression garments were ordered for Cases one and two (Haddenham, 2023).

Case three

Referred from Hospital two, the patient was a 48-year-old woman with a BMI of 24 and stage 2, grade 2, ER+ breast cancer. In 2019, she had a mastectomy, during which seven nodes were removed, of which one was positive. She also showed mild lymphoedema, 7 months prior; she was seen by local lymphoedema services for this and was prescribed Class 1 glove and sleeve, which is due for review. She also had AWS 2 weeks after surgery. Cords had been resolved by physiotherapy. She has also undergone radiotherapy. Due to a progressive, autoimmune skin reaction on her face and décolleté, Tamoxifen had been discontinued and replaced with Letrozole 6 weeks prior. Zoladex injection was prescribed every 3 months. Oedema was seen in the dorsum of the hand, thumb, index and middle finger, which was reactive to usual compression.

MLD was performed and overnight combined sleeve/mitten was ordered.

Axillary web syndrome

Further research was necessary, as Case three, who was not prescribed Ribociclib, had the same inflammatory symptoms. All three women had experienced AWS following surgery. Could this predispose patients to this type of oedema? One third of women develop AWS within 8 weeks of surgery. Slim women are more at risk (Jeong et al, 2021), The odds of AWS are 73% greater if you are over 60 years old. AWS predisposes a 44% greater risk of developing lymphoedema in the first year (Ryans et al, 2020).

Why is this? AWS occurs when an axillary lymph node is removed and the lymph vessels connected to it thrombose and harden into fibrous cords (Zhang et al, 2021). As the whole lymphatic pathway is affected, symptoms can be expected throughout its full length, from fingers to axilla. AWS often manifests as tingling, tightness and pain into the hand, even though the cords do not appear to reach that far (Dinas et al, 2019). The lymphatic system which is housed in the superficial fascia has been injured (Koehler et al, 2019), so stress of the whole arm could explain the responses.

Case four

Referred from Hospital one, the patient was a 57-year-old, with a BMI of 23; she had stage 2, ER+ and progesterone plus cancer of the right breast. Local wide excision, along with axillary clearance was conducted a year prior; a node was removed along side the reduction of the left breast. She also underwent radiotherapy. While there was no AWS, she had experienced post-op infections and 100 ml seromas in both breasts. Medications included Letrozole and Thyroxine. She presented with swift onset oedema of the right hand, thumb and index finger, potentially caused by an insect bite around 4 weeks prior. She remembered a slight mark on her hand but the 'bite' did not cause any reaction.

MLD was performed and Class 1, oversized sleeve plus glove were ordered. AWS did not explain this patient's presentation.

Case 5

Referred from hospital one the patient was a 59-year-old, with a BMI of 18 and stage 2, ER+ cancer of the right breast. She underwent a lumpectomy and the removal of three lymph nodes—two of which were positive. There was an axillary clearance after 6 weeks. She also had radiotherapy, and was diagnosed with AWS with three very large cords, 2 weeks after surgery. Some 5 weeks before referral, thumb and finger swelling developed with 'repetitive strain injury' of the right wrist. She was also suffering from Iatrogenic Dupuytren's Contracture of the contralateral left hand. She's currently not prescribed any medication, but was taking Letrozole for 6 months. However, it had been discontinued 3 weeks earlier, due to the contracture. After 5 weeks, the contracture had reversed and was not palpable. Subsequently, she was prescribed Exemestane, but within 5 days the contracture had returned and Exemestane was withdrawn.

Dupuytren's contracture

The contracture of the left hand was interesting because it had been attributed to Letrozole; showing that systemic myofascial reactions to the drug were likely. It had developed suddenly over 12 weeks, whereas contractures usually form slowly over months. Dupuytren's Contractures are characterised by thickening and shortening of the palmar fascia, into hardened cords with nodules, which pulls one or more fingers (usually the ring finger) towards the palm (Walthall et al, 2023). They are usually not curable or reversible. They are treated with steroid or enzyme collagenase injections, radiotherapy or surgery to remove them (Chen, 2011; Kadhum et al, 2017). However, the patient reported that since cessation of Letrozole, it had noticeably softened.

This development led to research into side effects of AIs and specifically, Letrozole.

The next day, a panicked call was received from Case four, whose symptoms had settled for 2 weeks using a Class 1, oversized glove. Overnight, she had experienced a severe, inflammatory reaction and balloon swelling of her whole arm. Cellulitis was eliminated, but Bioimpedance Spectrometry readings, which monitor extracellular fluid levels in limbs, showed a dramatic change from normal range (8%) at the last appointment, to oedematous (15%). Cessation of compression therapy was advised and a cotton sleeve/mitten was ordered.

All five women were asked if they had experienced any other hand symptoms, or seemingly unrelated tendon issues.

Additional myofascial symptoms

- Case one: Could not type for long without shooting pains
- Case two: Found it difficult to play the piano and suffered repetitive strain injury (RSI) whilst typing for work
- Case three: Experienced 'trigger finger' each morning, which had to be released before typing for work. RSI in both wrists
- Case four: Trigger finger of middle digit every morning on affected side. Nearly divulged at consultation but thought it was irrelevant, due to severe RSI in both hands from typing each day
- Case five: Dupuytren's Contracture, which completely reversed following 6 weeks' cessation from Letrozole.

Suspecting Letrozole as the only shared factor in all five women's symptoms, a literature review was undertaken to understand the mechanisms-of-action of AIs and if non-responsive, inflammatory oedemas could be explained by their use.

Oestrogen receptor positive: breast cancer and oestrogen

ER+ cancers rely on oestrogens to grow. There are three main types of oestrogen: oestrone, oestradiol and oestriol. Oestradiol is the most potent and dominates during the pre-menopausal stage of a woman's life, whereas oestrone plays a larger role following menopause. Oestriol is synthesised during pregnancy by the placenta. In pre-menopausal women, oestrogens are mostly made in the ovaries (Cui et al, 2013). AIs are ineffective with this patient group, unless the ovaries are suppressed, as gonadotrophin, Luteinising Hormone (LH), will induce compensatory ovarian oestrogen production (Early Breast Cancer Trialists' Collaborative Group (EBCTCG), 2022). This is why pre-menopausal Cases two and three take LH blocker, Zoladex, for ovarian suppression (Jonat, 2001).

Extra-gonadal oestrogen synthesis

Prior to 1974, it was thought that steroidal hormones could only be synthesised in endocrine glands (testes, ovaries or adrenals). Hemsell et al (1974), discovered that adipose tissue in men and post-menopausal women was a primary site for oestrogen synthesis, where adrenal androgens convert to oestrogen, using the enzyme aromatase in the final phase. Levels of circulating oestrogen in plasma from this source rise with advancing age (Cui et al, 2013). Extra-gonadal oestrogens also synthesise in healthy and malignant breast tissue, liver, pancreas, adrenal glands, brain, skin and sites yet to be identified (Barakat et al, 2016). Following menopause, these sites become the main source of oestrogen synthesis, especially the adipose tissue (Lønning, 2001).

Breast tissue has substantial aromatase activity, with aromatase in both stromal (connective tissue) and epithelial cells, as well as macrophages, which represent up to 25% of cells in breast tumours. Currently, 70% of breast tumours show localised oestrogen synthesis. The conversion rate is higher in obese women (Isnaldi et al, 2022), which increases the risk of both breast and endometrial cancers for obese, post-menopausal women (Miki et al, 2007).

Oestrogen suppression was developed as a key therapeutic intervention to starve ER+ cancers, using first and second generation AIs and Tamoxifen, a selective oestrogen receptor modulator (SERM) (Santen et al, 2009). Over the last 20 years, AIs have demonstrated superiority over Tamoxifen in improving outcomes for pre- and post-menopausal women by 30% (EBCTCG, 2022).

AIs reduce oestrogen production by 97–99%, by interrupting the conversion of androgens to oestrogen and blocking aromatase activity (Lønning, 2001), reducing circulating oestrogen to 10% of normal levels (Conejo et al, 2018). The current third generation AIs—Anastrozole and Letrozole—are reversible and non-steroidal, which stop the action of aromatase, while Exemestane is a steroid antagonist, which binds irreversibly to, and destroys the enzyme (Santen et al, 2009).

Who is prescribed aromatase inhibitors?

AIs are now standard treatment for both adjuvant and metastatic presentations. They are also used preventatively, to reduce the rate of breast cancer development in high-risk women, as well as in pre-menopausal women with a

high risk of reoccurrence, when combined with ovarian suppressants (Hyder et al, 2021).

Aromatase inhibitor-associated musculoskeletal syndome (AIMSS)

AIMSS is the most common adverse effect suffered by patients, with arthralgia (joint pain) reported by 47% of those taking AIs. Of these, 23.5% present with new symptoms and the remaining 23.5% have exacerbated pain from pre-existing symptoms. Onset is from 1.6 months, peaking at 6 months, when between 13–25% discontinue therapy (Gupta et al, 2020). While some tolerate switching to a different AI, the majority choose to cease treatment due to lack of relief (Hyder et al, 2021). This happened to Case five.

Those who discontinue AIs risk a 20% reoccurrence rate, compared to 11% for those who finish the recommended course (Hyder et al, 2021).

It is likely that AIMSS signifies very low oestrogen levels and could predict lower reoccurrence and improved disease-free survival (Hyder et al, 2021). In the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial, reoccurrence was 35% lower in participants who developed AIMSS at 3 months, than those who did not (Gupta et al, 2020). If a woman is <5 years from her last menstrual period, the residual circulating oestrogen could protect her from AIMSS (Grigorian and Baumrucker, 2022). However, obesity increases aromatase activity, which is associated with effective, but incomplete oestrogen suppression, with a higher risk of reoccurrence (Hyder et al, 2021; Shirdarreh and Pezo, 2021).

Those with BMI of >30 are predisposed to AIMSS. Pre-treatment levels of oestrogen are three times higher in women with BMI >35, than those with BMI of <25 and there is a rapid decline in oestrogen levels, inducing inflammatory symptoms (Huifang et al, 2022). Women with BMI of 25–30 had fewer symptoms than either those with higher or lower BMI, indicating that being overweight, but not obese, is also protective. Conversely, women with BMI of <25, without high levels of adipose tissue, suffer from oestrogen deprivation (Bowman and Lu, 2022). All five Cases have BMI below 25.

While AIMSS is extensively documented, the recognised symptoms are joint pain/morning stiffness, carpel tunnel syndrome (CTS), muscle pain or weakness, reduced grip strength and tenosynovitis (Hyder et al, 2021). There is scant research on inflammatory lymphoedema related to AIs, but the mechanisms are well understood.

Oestrogen deprivation, inflammation and reactive oedema

Oestrogen has an anti-inflammatory effect on the body, regulating the expression of pro-inflammatory cytokines like Interleukins 1/6 and Tumour Necrosis Factor-A and C-reactive protein. Their levels increase after menopause (Bauml et al, 2015). Oestrogen deprivation causes localised inflammation in peripheral, adipose tissue, with elevations of these cytokines apparent in the blood (Henry et al, 2010). MRIs have also shown fluid in tendon sheaths and thickening of flexor/extensor tendons of the hands (Morales et al, 2007). This correlates to the Dupuytren's Contracture symptoms of Case five.

The inflammatory process is mediated by mast cells positioned near blood vessels and lymphatics in connective tissues and skin. This allows them to respond to local stimuli rapidly, because of perceived damage or pathogen toxicity (Chen et al, 2017), leading to a massive release of inflammatory mediators and dramatic responses including angioedema, associated with allergic inflammation (Lichterman and Reddy, 2021).

This explains the perceived threat of conventional compression garments, which uniformly increased interstitial pressure and initiated the sudden, reactive mast cell responses in Cases one to four.

Cotton ribbed garments

The use of cotton, ribbed compression garments was extremely successful in all cases, swiftly reducing inflammation and calming reactive oedema. Conventional circular knit, Class 1 and 2 garments caused inflammatory symptoms. The anti-inflammatory mechanisms can be explained using the same physiological responses produced by lymphatic kinesiology tape applications, where the skin is lifted and inter-fascial space is created to relieve pressure and free lymphatic anchor filaments to open lymphatic vessels (Lipińska et al, 2007; Pop et al, 2014). Lymphatic flow is increased by dynamic, intermittent, manipulation of tissue pressures; pressure under the ribbing of the garment (and under the tape) is lower than the adjacent

Key points

- Letrozole is known to cause Aromatase Inhibitor Associated Musculoskeletal syndrome, which leads to 50% cessation of therapy, within 6 months; it can also be responsible for reactive, inflammatory lymphoedemas
- The use of conventional circular knit compression therapy was not tolerated; however, overnight, cotton, ribbed, combined sleeve and mitten proved swiftly anti-inflammatory and effectively reduced symptoms
- Overweight women, with a BMI of 25–30 are less likely to suffer musculoskeletal symptoms from AIs, as they have optimum levels of adipose tissue for complete oestrogen suppression, whereas slim women with BMI<25 suffer from oestrogen deprivation, which induces debilitating side effects.

CPD reflective questions

- How does the synthesis of oestrogen change as we age?
- Why are Cycline-Dependant Kinase 4/6 inhibitors prescribed alongside aromatase inhibitors?
- What causes Axillary Web Syndrome?
- What symptoms could suggest Aromatase Inhibitor Musculoskeletal Syndrome?
- How did the reactive, non-responsive oedemas occur?

skin, while pressure within the initial lymphatics is lower still, so interstitial fluid is drawn into the lymphatic system, enhancing drainage and reducing mast-cell reactivity because of the differentials in pressure (Kafa et al, 2015; Wu et al, 2015).

Conclusion

Having made evidence-based deductions that Letrozole was causing the adverse reactions, permission was gained and a table of findings was collated for all five patients and sent back to their consultants, with a request to undertake a risk/benefit analysis of Letrozole and medication reviews. Using this reflective approach, if a patient taking AIs develops non-responsive, inflammatory musculoskeletal/myofascial oedema, AIs should be considered as the possible trigger (Hyder et al, 2021).

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Barakat R, Oakley O, Kim H, Jin J, Ko CJ. Extra-gonadal sites of estrogen biosynthesis and function. BMB Rep. 2016;49(9):488–496. https://doi.org/10.5483/bmbrep.2016.49.9.141

Bauml J, Chen L, Chen J et al. Arthralgia among women taking aromatase inhibitors: is there a shared inflammatory mechanism with co-morbid fatigue and insomnia? Breast Cancer Res. 2015;17(1):89. https://doi.org/10.1186/s13058-015-0599-7

Bowman S, Lu H. Aromatase inhibitor-induced inflammatory myopathies: A case series. Joint Bone Spine. 2022;89(2):105308. https://doi.org/10.1016/j.jbspin.2021.105308

Chen L, Deng H, Cui H et al. Inflammatory responses and inflammation-associated diseases in organs. Oncotarget. 2017;9(6):7204–7218. https://doi.org/10.18632%2Foncotarget.23208

Chen NC, Srinivasan RC, Shauver MJ, Chung KC. A systematic review of outcomes of fasciotomy, aponeurotomy, and collagenase treatments for Dupuytren's contracture. Hand (N Y). 2011;6(3):250–255. https://doi.org/10.1007/s11552-011-9326-8

Conejo I, Pajares B, Alba E, Cuesta-Vargas AI. Effect of neuromuscular taping on musculoskeletal disorders secondary to the use of aromatase inhibitors in breast cancer survivors: a pragmatic randomised clinical trial. BMC Complement Altern Med. 2018;18(1):180. https://doi.org/10.1186/s12906-018-2236-3

Cui J, Shen Y, Li R. Estrogen synthesis and signaling pathways during aging: from periphery to brain. Trends Mol Med. 2013;19(3):197–209. https://doi.org/10.1016%2Fj.molmed.2012.12.007

Dinas K, Kalder M, Zepiridis L, Mavromatidis G, Pratilas G. Axillary web syndrome: incidence, pathogenesis, and management. Curr Probl Cancer. 2019;43(6):100470. https://doi.org/10.1016/j.currproblcancer.2019.02.002

Ding L, Cao J, Lin W et al. The roles of cyclin-dependent kinases in cell-cycle progression and therapeutic strategies in human breast cancer. Int J Mol Sci. 2020;21(6):1960. https://doi.org/10.3390%2Fijms21061960

Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Aromatase inhibitors versus tamoxifen in premenopausal women with oestrogen receptor-positive early-stage breast cancer treated with ovarian suppression: a patient-level meta-analysis of 7030 women from four randomised trials. Lancet Oncol. 2022;23(3):382-392. https://doi.org/10.1016/s1470-2045(21)00758-0

Finnsdottir S, Sverrisdottir A, Björnsson ES. Hepatotoxicity associated with ribociclib among breast cancer patients. Acta Oncol. 2021;60(2):195–198. https://doi.org/10.1080/0284186x.2020.1853228

Grigorian N, Baumrucker SJ. Aromatase inhibitor-associated musculoskeletal pain: An overview of pathophysiology and treatment modalities. SAGE Open Med. 2022;10:20503121221078722. https://doi.org/10.1177/20503121221078722

Gupta A, Henry NL, Loprinzi CL. Management of Aromatase Inhibitor-Induced Musculoskeletal Symptoms. JCO Oncol Pract. 2020;16(11):733–739. https://doi.org/10.1200/op.20.00113

Haddenham. Comfiwave, Compression to drift off in. 2023. https://hadhealth.com/assets/info-sheets/CWLF-006a-NPv4-comfiwave-brochure-comp.pdf (accessed 14 August 2023)

Hemsell DL, Grodin JM, Brenner PF, Siiteri PK, MacDonald PC. Plasma precursors of estrogen. II. Correlation of the extent of conversion of plasma androstenedione to estrone with age. J Clin Endocrinol Metab. 1974;38(3):476-479. https://doi.org/10.1210/jcem-38-3-476

Henry NL, Pchejetski D, A'Hern R et al. Inflammatory cytokines and aromatase inhibitor-associated musculoskeletal syndrome: a case-control study. Br J Cancer. 2010;103(3):291–296. https://doi.org/10.1038/sj.bjc.6605768

Huifang L, Jie G, Yi F. Neuro-immune-endocrine mechanisms with poor adherence to aromatase inhibitor therapy in breast cancer. Front Oncol. 2022;12:1054086. https://doi.org/10.3389/fonc.2022.1054086

Hyder T, Marino CC, Ahmad S, Nasrazadani A, Brufsky AM. Aromatase inhibitor-associated musculoskeletal syndrome: understanding mechanisms and management. Front Endocrinol (Lausanne). 2021;12:713700. https://doi.org/10.3389/fendo.2021.713700

Isnaldi E, Richard F, De Schepper M et al. The association between adiposity and anti-proliferative response to neoadjuvant endocrine therapy with letrozole in post-menopausal patients with estrogen receptor positive breast cancer. NPJ Breast Cancer. 2022;8(1):90. https://doi.org/10.1038/s41523-022-00453-7

Jeong S, Song BJ, Rhu J, Kim C, Im S, Park GY. A Risk factor analysis of axillary web syndrome in patients after breast cancer surgery: a single center study in Korea. Ann Rehabil Med. 2021;45(5):401–409. https://doi.org/10.5535%2Farm.21092

Jonat W. Goserelin (Zoladex)--its role in early breast cancer in pre- and perimenopausal women. Br J Cancer. 2001;85 Suppl 2(Suppl 2):1–5. https://doi.org/10.1054/bjoc.2001.1981

Kadhum M, Smock E, Khan A, Fleming A. Radiotherapy in Dupuytren's disease: a systematic review of the evidence. J Hand Surg Eur Vol. 2017;42(7):689–692. https://doi.org/10.1177/1753193417695996

Kafa N, Citaker S, Omeroglu S, Peker T, Coskun N, Diker S. Effects of kinesiologic taping on epidermal-dermal distance, pain, edema and inflammation after experimentally induced soft tissue trauma. Physiother Theory Pract. 2015;31(8):556–561. https://doi.org/10.3109/09593985.2015.1062943

Koehler LA, Haddad TC, Hunter DW, Tuttle TM. Axillary web syndrome following breast cancer surgery: symptoms, complications, and management strategies. Breast Cancer (Dove Med Press). 2018;11:13–19. https://doi.org/10.2147/bctt.s146635

Lichterman JN, Reddy SM. Mast Cells: A new frontier for cancer immunotherapy. Cells. 2021;10(6):1270. https://doi.org/10.3390%2Fcells10061270

Lipi ska A, Śliwiński Z, Kiebzak W, Senderek T, Kirenko J. Influence of kinesiotaping application on lymphoedema of an upper limb in women after mastectomy. Polish Journal of Physiotherapy. 2007;7:258-269.

Lønning PE. Aromatase inhibitors and inactivators in breast cancer. BMJ. 2001;323(7318):880-881. https://doi.org/10.1136%2Fbmj.323.7318.880

Miki Y, Suzuki T, Tazawa C et al. Aromatase localization in human breast cancer tissues: possible interactions between intratumoral stromal and parenchymal cells. Cancer Res. 2007;67(8):3945–3954. https://doi.org/10.1158/0008-5472.can-06-3105

Morales L, Pans S, Paridaens R et al. Debilitating musculoskeletal pain and stiffness with letrozole and exemestane: associated tenosynovial changes on magnetic resonance imaging. Breast Cancer Res Treat. 2007;104(1):87–91

Murphy CG, Dickler MN. The Role of CDK4/6 inhibition in breast cancer. Oncologist. 2015;20(5):483–490. https://doi.org/10.1634/theoncologist.2014-0443

Pop TB, Karczmarek-Borowska B, Tymczak M, Hałas I, Banaś J. The influence of Kinesiology Taping on the reduction of lymphoedema among women after mastectomy—preliminary study. Contemp Oncol (Pozn). 2014;18(2):124–129. https://doi.org/10.5114/wo.2014.40644

Presti D, Quaquarini E. The PI3K/AKT/mTOR and CDK4/6 Pathways in Endocrine Resistant HR+/HER2- Metastatic Breast Cancer: Biological Mechanisms and New Treatments. Cancers (Basel). 2019;11(9):1242. https://doi.org/10.3390/cancers11091242

Ryans K, Davies CC, Gaw G, Lambe C, Henninge M, VanHoose L. Incidence and predictors of axillary web syndrome and its association

with lymphedema in women following breast cancer treatment: a retrospective study. Support Care Cancer. 2020;28(12):5881–5888. https://doi.org/10.1007/s00520-020-05424-x

Santen RJ, Brodie H, Simpson ER, Siiteri PK, Brodie A. History of aromatase: saga of an important biological mediator and therapeutic target. Endocr Rev. 2009;30(4):343–375. https://doi.org/10.1210/er.2008-0016

Scott SC, Lee SS, Abraham J. Mechanisms of therapeutic CDK4/6 inhibition in breast cancer. Semin Oncol. 2017;44(6):385-394. https://doi.org/10.1053/j.seminoncol.2018.01.006

Shirdarreh M, Pezo RC. Impact of obesity on clinical outcomes in hormone receptor-positive breast cancer: a systematic review. Breast Cancer. 2021;28(3):755–764. https://doi.org/10.1007/s12282-020-01213-w

Skafida E, Andrikopoulou A, Terpos E et al. Impact of CDK4/6 inhibitors on aromatase inhibitor-associated musculoskeletal syndrome (AIMSS) in the adjuvant setting. Breast J. 2023;2023:3614296. https://doi.org/10.1155/2023/3614296

Walthall J, Anand P, Rehman P. Dupuytren Contracture. Treasure Island (FL): StatPearls Publishing; 2023

Watt AC, Goel S. Cellular mechanisms underlying response and resistance to CDK4/6 inhibitors in the treatment of hormone receptor-positive breast cancer. Breast Cancer Res. 2022;24(1):17. https://doi.org/10.1186/s13058-022-01510-6

Wu WT, Hong CZ, Chou LW. The Kinesio Taping Method for Myofascial Pain Control. Evid Based Complement Alternat Med. 2015;2015:950519. https://doi.org/10.1155%2F2015%2F950519

Zhang W, Li J, Liang J, Qi X, Tian J, Liu J. Coagulation in lymphatic system. Front Cardiovasc Med. 2021;8:762648. https://doi.org/10.3389%2Ffcvm.2021.762648