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Case Study

Neoadjuvant chemotherapy and fertility preservation in breast cancer treatment

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Key Learning Points

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- Breast cancer is the most common cancer in the UK[1], and one of the most treatable.
- Adjuvant and neoadjuvant chemotherapy constitute a key aspect of breast cancer treatment, alongside surgical and radiotherapy. Several factors impact the choice between adjuvant and neoadjuvant chemotherapy, including age, tumour size, receptor profile, amenability to hormonal treatment and fertility preservation.
- Triple negative breast cancer (TNBC), denoting the lack of oestrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) expression, is an aggressive form of the disease not amenable to hormonal or biological therapy. Neoadjuvant chemotherapy is often preferred to adjuvant chemotherapy in TNBC.
- Proposed advantages of neoadjuvant chemotherapy in favour of adjuvant chemotherapy include reducing tumour size to improve outcomes from surgical excision, in vivo assessment of response, window of opportunity studies and further systemic treatment for residual disease. However, the evidence for improved survival outcomes from neoadjuvant compared with adjuvant chemotherapy is not definitive, and patient involvement in making this decision is paramount.
- This case report highlights the importance of fertility considerations in the decision between neoadjuvant and adjuvant chemotherapy, and proposes that as recent trends showing increased age of socioeconomic independence are paralleled by the rising age of primigravida in the UK, fertility considerations may be of higher priority for nulliparous premenopausal women making this decision.

Introduction

Breast cancer accounts for the majority of cancers in women worldwide, and the most common cancer overall in the UK[1]. In the absence of distant metastases, breast cancer is treatable with curative intent[2], typically with a combination of surgical and medical interventions[3]. Adjuvant and neoadjuvant chemotherapy, denoting post-operative and pre-operative chemotherapy respectively, are commonly delivered alongside surgery and radiotherapy, hormonal therapy and Herceptin in breast cancer treatment[4].

This report will discuss the implications of neoadjuvant chemotherapy for women of childbearing age for whom fertility preservation is a pressing concern. This will be illustrated by a case in which the time taken for a patient with newly diagnosed invasive breast cancer to reach a decision on fertility treatment prior to neoadjuvant chemotherapy ultimately delayed cancer treatment, despite surgery being an available initial treatment option. Various surgical and chemotherapeutic options for breast cancer will be outlined, followed by an exploration of the available literature on neoadjuvant chemotherapy in breast cancer treatment. Finally, the illustrative case will be reviewed in the context of the literature to propose a new perspective on neoadjuvant chemotherapy in premenopausal women for whom fertility preservation is a matter of concern.

Case History

AT, a 37-year-old zookeeper, was referred by her GP to the breast clinic for investigation of a palpable breast lump with associated pain in February 2021. She had incidentally discovered the lump one month previously on palpation of a bruise over her ribs following a fall. On examination, a 25 mm rounded, smooth, firm mass was palpable in the upper outer quadrant of her right breast. Evidence of right lateral chest wall pain was also found, for which AT was advised to take analgesic medications and was given patient educational materials on breast pain and

costochondritis.

AT reported no previous history of breast disease, and no family history of any breast or ovarian cancer. She was premenopausal, nulliparous, and had previously taken the oral contraceptive pill for approximately 10 years. Due to her young age, the absence of significant risk factors for breast cancer and the nature of the lump on examination, the lump was clinically considered to be a breast cyst. This was confirmed by an ultrasound scan showing a thick-walled cyst at the symptomatic site. Yellow fluid was aspirated and discarded from the cyst, however the cyst wall remained following aspiration, measuring 23 mm x 9 mm, therefore an ultrasound-guided core biopsy of the cyst wall was performed.

Histopathological analysis of the biopsy revealed a grade 3 triple negative invasive ductal carcinoma underlying the aspirated cyst. In a subsequent breast clinic appointment, it was noted that the palpable lump appeared amenable to breast conserving surgery on clinical examination. A series of further investigations were arranged, including mammography, MRI and CT imaging to characterise and stage the cancer. These confirmed a 25 mm peripherally enhancing right breast nodule consistent with the primary tumour, and found no metastasis or lymphadenopathy. Following an MDT discussion, AT was subsequently referred to oncology to discuss neo-adjuvant chemotherapy. She was also referred to a fertility clinic to discuss the implications of chemotherapy on her ability to have children in future, and to genetic testing for BRCA1, BRCA2 and PALB2. These genetic tests were negative.

At her oncology clinic appointment, AT agreed to undergo neoadjuvant chemotherapy, and to do so within the ongoing PARTNER trial investigating the addition of Olaparib to the neoadjuvant chemotherapy regimen for invasive breast cancer. She was also informed that she could have breast conserving surgery with sentinel node biopsy. AT expressed her desire to preserve fertility if possible as she was unsure if she wanted to have children in the future, and was therefore referred to her GP for commencement of a gonadotropin releasing hormone (GnRH) agonist, Zoladex, for fertility preservation throughout chemotherapy. She was, however, also advised that she should wait 2 to 3 years before trying to become pregnant after chemotherapy, and as she will be 40 years old by that time, her fertility may already be diminished by then, hence she may be unable to have children.

AT then attended a fertility clinic, where she was informed of her fertility options. The choice of in vitro fertilisation (IVF) treatment before neoadjuvant chemotherapy was offered, thus improving her chances of pregnancy following her cancer treatment. Following this discussion, AT was unsure about her fertility preservation preference and remained so until the end of March 2021. On the 29th March 2021, AT informed the fertility team of her decision to commence egg harvesting for IVF treatment. She was consequently advised by the oncology team that as she would be unable to commence chemotherapy while egg harvesting was taking place. In order to avoid any further delay of her cancer treatment, she was advised to forgo neoadjuvant chemotherapy in favour of primary surgery followed by adjuvant chemotherapy, allowing for egg harvesting alongside surgery. Her Zoladex treatment was to be deferred till after egg harvesting, but prior to adjuvant chemotherapy.

AT was thus referred back to the breast surgery team, prior to which she expressed concern to the cancer specialist nurse that the lump appeared to have grown. At her breast clinic appointment, it was noted that the lesion remained palpable, but now occupying the majority of the upper outer quadrant of the right breast. Following a discussion of surgical options, AT was offered a wide local excision with sentinel lymph node biopsy through a lateral mammoplasty approach. On excision, sentinel nodes were found negative for cancerous cells. Histopathology revealed a 30 mm grade 3 triple negative invasive ductal carcinoma (NST) displaying no lymphovascular invasion with clear margins. AT made an uncomplicated recovery from the procedure and is currently undergoing IVF treatment, following which she will commence adjuvant chemotherapy and radiotherapy.

Discussion

Due to the ongoing fertility discussions delaying commencement of neoadjuvant chemotherapy and the subsequent change in treatment plan to a primary surgical intervention, AT missed her cancer breach date by 9 days. The time between discussing treatment and fertility options and making the decision to commence IVF was 17 days. As her tumour was triple negative, denoting the lack of oestrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) expression, it is not amenable to hormone therapies targeting these receptors. Triple negative breast cancer (TNBC) is more aggressive than other breast cancer types[5], so early treatment is of particular importance to patients like AT.

Considering the dilemma of fertility women of childbearing age face, when considering chemotherapeutic treatment for cancer and the effectiveness of breast surgery as first line treatment prior to chemotherapy, do the advantages of neoadjuvant chemotherapy in favour of adjuvant chemotherapy outweigh the risks of potential delays to treatment as fertility decisions are made?

Surgical interventions for breast cancer

Surgery is always indicated in early breast cancer without metastases in patients deemed operable, however when surgery should take place in relation to systemic therapies is largely guided by the type and molecular characteristics of the tumour[2]. Metastatic breast cancer is primarily managed by systemic treatment, though there exists some role for local treatment, including breast surgery, to manage both the primary disease and metastases for palliation[6]. This report will not discuss treatment for metastatic breast cancer, focussing instead on early breast cancer as illustrated in the above case history.

Surgery for early breast cancer is broadly divided into 2 categories: mastectomy and breast conserving therapy (BCT), with the choice depending on both the type and extent of the tumour being excised. When BCT is combined with radiotherapy, survival is at least equivalent between BCT and mastectomy in early invasive breast carcinoma, and in some cases BCT is reported to exert a survival advantage over mastectomy[7–10]. Instances where BCT is not possible include multicentric disease and large tumour size relative to breast size among others[11], in which case mastectomy is preferred.

Axillary evaluation is another important aspect of surgical interventions for breast cancer. Axillary lymph node involvement signifies the propensity of a tumour to spread[12], the likelihood of which increases with tumour size[13]. Therefore, sentinel lymph node biopsy is often conducted alongside tumour excision in patients with axillary nodes preoperatively deemed negative for signs of

tumour involvement[14].

The role of chemotherapy in breast cancer treatment

Adjuvant chemotherapy in breast cancer treatment has been in place since the 1970s, and has improved overall and progression free survival following breast tumour surgery[15]. The introduction of neoadjuvant chemotherapy followed shortly thereafter in the 1980s[16], but has proven more controversial than adjuvant chemotherapy in subsequent decades to the present day. In 2018, the Association of Breast Surgery (ABS) proposed that neoadjuvant chemotherapy still constitutes a key gap in breast surgery research, including in identifying patients most likely to benefit from the treatment[17].

The original rationale for neoadjuvant chemotherapy was to make surgical resection possible in locally advanced tumours considered inoperable, however one randomised control trial (RCT) showed no survival benefit for this indication[18] in a short 25-month follow up period. Nonetheless, this paved the way for investigations on the potential benefits of neoadjuvant chemotherapy in smaller, operable tumours[19,20]. Proposed advantages of neoadjuvant chemotherapy in favour of adjuvant chemotherapy include reducing the extent of necessary surgery by reduction of tumour size, and the early identification of tumours amenable to systemic treatment as a tool to guide potential adjuvant therapies and to establish prognosis[21]. As differing neoadjuvant chemotherapy regimens, for example to include immune checkpoint inhibitor combinations, Oleparib and cisplatin-based therapies are evaluated in clinical trials for triple negative breast cancer, a further emerging advantage may be greater choice of potentially more effective treatments at the neoadjuvant, compared with the adjuvant, stage[22–24].

Neoadjuvant chemotherapy has therefore emerged in recent decades as an established systemic treatment for non-metastatic invasive breast cancer[25]. Preoperative chemotherapy improves the rates of breast conservation and, consequently, cosmetic results[26]. There are also suggestions that it may result in fewer post-operative procedures such as re-excision[27]. Overall survival, however, is not improved by neoadjuvant chemotherapy, despite allowing for earlier initiation of systemic therapy. A 2005 meta-analysis followed by a 2007 Cochrane review found comparable overall and disease-free survival rates for adjuvant and neoadjuvant therapy[28,29]. Despite this, neoadjuvant chemotherapy continues to be an established and often favoured avenue for early breast cancer treatment. It is notable that these studies did not distinguish between breast cancer subtypes, even though they are biologically distinct.

One instance in which neoadjuvant chemotherapy is favoured is for patients with triple negative invasive breast carcinoma[30]. Neoadjuvant chemotherapy improves 3-year survival by 26% in patients who have a full pathological response compared with those with residual disease[31]. Triple negative tumours are in fact more likely to achieve a full pathological response, compared with other breast cancer subtypes[31], so neoadjuvant chemotherapy is more likely to improve outcomes in these cases. However, a full pathological response is not seen in the majority of triple negative breast cancer cases. Therefore, one goal of research in this field is to identify the minority of triple negative tumours that stand to benefit from neoadjuvant chemotherapy[32]. A further goal is to increase the number of patients with triple negative cancer that achieve a complete pathological response. The recent BrighTNess trial has demonstrated that altering the neoadjuvant chemotherapy regimen results in an improvement in the proportion of patients with triple negative breast cancer who achieve a complete pathological response[23], and that neoadjuvant chemotherapy increases eligibility for breast conserving surgery in stage II to III triple negative breast cancer[24]. The ongoing PARTNER trial, to which AT was initially recruited, may further identify improvements to the standard neoadjuvant chemotherapy regimen for triple negative breast cancer.

Neoadjuvant chemotherapy also allows early monitoring of tumour response to chemotherapeutic agents, allowing more targeted therapy following surgery and in residual disease. Further, half of triple negative tumours are likely to recur within 5 years[33], and neoadjuvant treatment allows early targeting of undetectable tumour cells at distant sites, thus reducing the risk of recurrence. Neoadjuvant chemotherapy therefore continues to be offered to patients with triple negative tumours like AT.

One significant risk of neoadjuvant chemotherapy is that it delays surgery. In patients with aggressive triple negative tumours not responsive to chemotherapy, this delay may be enough to allow tumour expansion and invasion to the point of inoperability, where previously it was small enough to have been excised with curative potential. Chemotherapy can, however, be stopped at any point in favour of surgery throughout the neoadjuvant cycle by monitoring the tumour clinically and by MRI scans. A further cause for delay, as the case history in this report shows, is the time taken to decide between surgery and neoadjuvant chemotherapy as the appropriate primary treatment. In this case, such a delay was precipitated by decisions on fertility, leading to the worst-case scenario in any new cancer diagnosis: delay with no treatment at all. According the online tool NHS Predict[34], AT's likelihood of 10-year survival at diagnosis was 78% with only surgery, rising to 84% with 3rd generation chemotherapy. Accounting for the increase in tumour size, at the time of surgery AT's likelihood of 10-year survival was 75%, rising to 82% with 3rd generation chemotherapy. It is therefore important to note that while the tumour was substantially larger at excision than at diagnosis, the relative impact of treatment delay on AT's likelihood of survival was small. Nonetheless, timely treatment is essential to improving cancer survival outcomes, so any delay to treatment, including fertility indecision, warrants consideration.

The implications of neoadjuvant chemotherapy on fertility

The negative impacts of chemotherapy on fertility are diverse and well documented, depending, among other factors, on the gonadotoxicity of the chemotherapeutic agents and the dose used[35]. The 10-year survival of women with breast cancer in the UK is 81%, and of women aged 15-39, 77%[36]. The average age of primigravida in the UK has been gradually increasing since the 1970s, now standing at 30.7[37]. It is reasonable to expect a continuation of this trend, and as breast cancer constitutes the majority of cancers in women aged 25-49[38], this suggests that the number of women with breast cancer for whom fertility preservation is a significant issue is likely to rise as well. Therefore, fertility preservation should be a central issue in further research and recommendations on neoadjuvant chemotherapy.

There are no known negative effects of pregnancy following breast cancer treatment on prognosis[39]. On the contrary, one meta-analysis found an increase in overall

survival in women who became pregnant after breast cancer[40], and was followed by a retrospective cohort study alluding to a similar trend, though to a lesser extent[41]. Due to confounding factors including selection bias, whether or not pregnancy following breast cancer is truly prognostically protective is unclear[42], however it is certainly considered safe and patients are therefore routinely counselled on fertility preservation when discussing treatment options.

For women with a partner or those planning on using sperm donors, the most effective way to preserve fertility through chemotherapy treatment is by embryo cryopreservation after IVF. If those criteria are not met, oocyte cryopreservation is preferred alternative. Both of these can necessitate a delay to chemotherapy treatment initiation as patients undergo ovarian stimulation to produce retrieve mature oocytes. If such a delay constitutes a high risk to prognosis, for example where chemotherapy is the primary treatment option for an aggressive cancer, immature oocyte cryopreservation is also possible[43]. Ovarian tissue cryopreservation is a further, newer, promising strategy for fertility preservation, but which currently has low usage rates[44].

It is important to note that many women become pregnant after chemotherapy without any treatment, particularly if they undergo treatment at a younger age, when they have a higher chance of retaining fertility. More conservative fertility preservation options are also available, including ovarian suppression by GnRH agonists. Although GnRH agonists initially stimulate the release of follicle-stimulating hormone (FSH) and luteinising hormone (LH), their long term effect is downregulation of GnRH receptors and desensitisation and subsequent suppression of FSH, resulting in the suppression of ovarian function[42]. Chemotherapy is typically most toxic to tissues with a rapid cell turnover, therefore the rationale for GnRH agonist use is ovarian protection from gonadotoxic chemotherapeutic agents[45]. GnRH agonists have indeed been shown to preserve ovarian function following chemotherapy[46,47], and so are a reasonable option for those unable or unwilling to explore more invasive fertility preservation options.

The theoretical risk of cancer progression and relapse from ovarian stimulation and hormonal treatments has led to some caution in recommending fertility preservation for patients with breast cancer in the past. Despite initial concerns, ovarian stimulation does not generally appear to negatively impact relapse rates and overall survival from breast cancer[48–51], however long-term robust analysis of the impacts of fertility preservation on different breast cancer subtypes is lacking.

The future of breast cancer treatment in women of childbearing age

The patient in the case history presented here, AT, was initially uncertain of her desire to have children in future. As discussed above, neoadjuvant chemotherapy is a common treatment pathway for patients with triple negative invasive breast cancer. Considering her uncertainty and her age, 7 years above the average age for primigravida in the UK, fertility preservation may have seemed of low priority from her oncologist's perspective. Upon consideration, however, fertility preservation emerged as a high priority for AT. AT described that she and her partner had only recently moved into their own home, having previously lived with AT's parents. She had not considered pregnancy a serious possibility before the move, but was in a stable long-term relationship and had not ruled it out as an option. In unfortunate timing, her cancer diagnosis coincided with her long-anticipated acquisition of independence, when having children became possible.

The past four decades has seen a trend reversal from increasing to decreasing rates of homeownership of people ages 16-64, accompanied by a parallel expansion in the private rental sector[52]. These inter-generational housing inequalities parallel intra-generational wealth inequalities[53], resulting in a rise in young adults aged 20-34 living with their parents[54]. The progressive loss of financial independence in the young adult population in the UK, alongside other social factors including barriers to career progression and workplace stigmas around having children, have contributed to the progressively rising age of primigravida[37]. This has inevitable implications for fertility preservation in nulliparous premenopausal women with breast cancer. The belief that fertility is a low priority issue in nulliparous premenopausal women with naturally diminishing fertility is an unfair assumption in the current climate, where having children is often economically unfeasible for young women. Novel neoadjuvant regimens that improve rates of patients achieving a complete pathological response and thus improve the survival advantage of neoadjuvant chemotherapy[23], alongside fertility preservation regimens that allow commencement at any cycle stage[55] could potentially remove the ambiguity of the decision to commence neoadjuvant chemotherapy for patients with childbearing potential. However, at present, fertility considerations present a strong reason to favour surgery, not neoadjuvant chemotherapy, as the initial treatment modality for breast cancer, followed by adjuvant chemotherapy and radiotherapy.

As discussed, even in the case of aggressive triple negative invasive breast carcinomas, the benefits of neoadjuvant chemotherapy are not unanimous. The available literature suggests that neoadjuvant chemotherapy in triple negative invasive breast cancer confers a survival benefit only in those that have a full pathological response[31], and the overall survival is comparable between adjuvant and neoadjuvant chemotherapy administration to women with breast cancer[29]. The potential harm of treatment delay from outdated assumptions on fertility at higher ages therefore outweighs the potential benefit conferred in the minority of women with the triple negative disease that may have a full pathological response. Until further research definitively identifies patients for whom neoadjuvant chemotherapy confers survival advantage, it would be reasonable to adapt practice to favour surgery followed by adjuvant chemotherapy and radiotherapy in all women for whom fertility is a potential concern, ensuring an active partnership in breast cancer care that accounts for patients' wishes in conjunction with cancer management.

Conclusion

The best available evidence for neoadjuvant chemotherapy in favour of adjuvant chemotherapy alongside surgery in the treatment of breast cancer indicates comparable overall and disease-free survival between the two treatment options. Neoadjuvant chemotherapy confers some benefit in triple negative breast carcinoma, but as far as is presently known, not for the majority of triple negative breast cancer cases. As the outlined case illustrates, the potential for delay to curative treatment is one considerable disadvantage of neoadjuvant chemotherapy. While this can be true even if neoadjuvant chemotherapy is immediately commenced, in the instance of tumour insensitivity to the chemotherapeutic agents administered, this can also be precipitated by the time taken for patients

to consider fertility preservation choices, as was true in the case presented. Considering the continuing upward trend observed in the average age of primigravida in recent years, the time required for patients to decide on fertility preservation options should be factored into the treatment of premenopausal women. These trends should also be considered in NHS IVF treatment provision, which currently does not extend to patients like AT in many parts of the UK. If patients express uncertainty about their fertility options, then surgery should be immediately organised to remove the tumour, thus allowing time for fertility considerations without compromising prompt treatment and consequent curative potential.

Conflicts of interest
None.

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Consent
The patient has consented to the publication of this case study.

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