The treatment of a ductal carcinoma

Introduction

The treatment of ductal carcinoma in situ (DCIS) has changed dramatically in the last decade. Since the introduction of national mammographic screening programmes the clinical presentation of DCIS has increased over the last decade. Before the development of screening programmes DCIS was diagnosed in a small proportion of patients presenting with a palpable mass or pathological nipple discharge. Until recently the standard treatment for DCIS was mastectomy but recent studies have found that DCIS can be treated with alternative, more targeted therapy, these will be discussed later on in the essay.

Epidemiology

Breast cancer remains the most common malignant disease affecting women in the UK and United States. Since 1990 Worldwide, the identification of DCIS is now most frequently encountered in asymptomatic women; the incidence in Western Countries has had a ‘ four-fold’ increase, especially in women of screening age (women aged 50 years or older). It has been reported that approximately one fifth of all screen detected breast cancers are now DCIS. However although there has been an increase in the diagnosis of DCIS, overall breast cancer rates have reached a plateau since 1990, most noticeably being the decline in mortality rates from breast cancer especially in younger women and women with oestrogen receptor (ER) positive disease. This is a result of the early detection with screening programmes and the development of more effective adjuvant therapy.

Aetiology

Risk factors for invasive breast cancer (IBC) and DCIS are similar, including a family history of breast cancer, prior breast biopsies, nulliparity, and late age of first pregnancy. The strongest risk factor for developing breast cancer (after gender) is age; the older the woman, the higher her risk (25). A family history of breast cancer increases the risk especially if the first degree relative is affected as it approximately doubles the risk compared to a woman with no family history. In addition to this, the risk is higher if the relative is diagnosed under the age of 50. In regards to the susceptibility of breast cancer, mutations in BRCA1 and BRCA2 account for the majority of families with four or more relatives affected. There has also been a link to the use of exogenous hormones and breast cancer, but users of the combined oral contraceptive pill tend to be of a younger age therefore lowers their risk of developing breast cancer.

Pathophysiology

Pre-existing benign lesions such as atypical ductal hyperplasia (ADH), atypical lobular hyperplasia and lobular carcinoma in situ (LCIS) are thought to be the cause of the development of most invasive breast cancers. However DCIS is regarded as a pre-invasive malignant lesion. DCIS is defined as an abnormal proliferation of epithelial cells that do not trespass the basal membrane of the breast ductal system. It is a heterogenous group of diseases with different histology and prognosis. DCIS can be classified into two different models, the first; Van Nuys classification uses scores from 1 to 3 for tumour size, margins, histology and age. The sum of these scores is associated with the risk of local failure i. e. patients with higher scores have a higher risk of local failure despite having radiotherapy and thus may

benefit from mastectomy. The other classification EORTC uses primary and secondary criteria. The primary criteria include nuclei, chromatin, nucleoli and mitosis. Each of these factors can be categorised into intermediate or poorly differentiated based on chromatin distribution. However a more practical classification separates the poorly differentiated group that behaves aggressively and a well differentiated group that has a better outcome. At the molecular level they are characterised by high expression of HER2, Cox-2, loss of heterozygosity in chromosome 17 and mutations in p53.

The majority of all breast cancers worldwide are formed from either ductal or lobular subtypes. Ductal subtype constitutes to 40-75% of all diagnosed cases and there are two models which have been proposed to show the initiation, transformation and progression of breast cancer. Figure 1 on the next page illustrates these two models.

Diagram A illustrates the typical model of cancer progression which suggests that the development of neoplasm initially starts in normal epithelium and then proceeds to flat epithelia atypia (FEA), evolves to atypical ductal hyperplasia (ADH), and then advances to ductal carcinoma in situ (DCIS) which then culminates as invasive ductal carcinoma (IDC). Diagram B represents usual ductal hyperplasia (UDH) instead of FEA as the direct precursor to ADH. However recent studies , have shown that UDH has a distinct molecular profile compared to FEA and thus probably represents a dead end. Diagram C represents multi-step progression from normal epithelium to invasive lobular carcinoma (ILC).

The events which occur during the pre-invasive stages of breast cancer are similar to those observed for IDC. In low-grade IDC there are fewer overall chromosomal aberrations such as frequent loss of 16q as seen in DCIS, whereas in high-grade IDC the tumours display recurrent losses of 8p, 11q, 13q, 1p and 18q. In addition to this there is a recurrent gain of 8q, 17q, 20q and 16p, therefore showing more chromosomal aberrations. There is a similar recurrent loss of chromosome 16q in low-grade DCIS and chromosome 13q loss and high-levels of amplifications of 17q12 and 11q13 in high-grade DCIS . It is evident that low-grade and high-grade DCIS appear to arise from two distinct pathways as figure 2 shows; this comes from a comparative analysis of gene expression of ADH and DCIS. A study done by Ma et al , demonstrated that there was no transcriptional changes transpiring between the preinvasive and invasive stages. It also became evident that the transition from preinvasive to invasive is related with quantitative gene expression rather than qualitative. Therefore quantitative gene expression is more outstanding in high-grade lesions. In addition to this Ma et al also verified that it is the unique gene expression signatures which are related with different tumour grades regardless of tumour stage.

As you can see from figure 2, the majority of breast cancers are classified into either high-grade or low-grade type pathways. The difference in these two pathways is the difference in chromosomal aberrations as mentioned earlier. Also the expression of oestrogen (ER+) and progesterone (PR+) receptors is used when selecting patients with breast cancer for endocrine hormone therapy . The reasoning for this is that oestrogen promotes tumour growth via the ER. This is quite significant as high-grade lesions possess a

lack of oestrogen and progesterone receptors (ER- and PR-) thus specific hormone therapy would not be of benefit. This will be discussed later on when analysing the benefit of hormone therapy in DCIS.

Diagnostic techniques and grading/staging of breast cancer

DCIS is diagnosed by clinical findings, incidentally or after plastic surgery, however DCIS is generally recognised as a precursor for invasive breast cancer and recurrence rates for younger women are high compared to women over 40 years. The gold standard test for screening is mammography (26). If a suspicious area is found then a needle biopsy is performed to confirm any abnormal cells. Ultrasound can be performed on women who have denser breasts and found no abnormality on mammography but have a strong family history of breast cancer.

Staging of breast cancer usually refers to the size of the tumour and the affected lymph nodes surrounding it. DCIS is sometimes described as stage 0. The table below illustrates the stages 1 to 4 of invasive breast cancer:

Stages	Features
1	Tumour size < 2cm, axillary lymph nodes are not affected

	and no signs of metastases
2	Tumour size between 2cm and 5cm, axillary lymph nodes are affected. No signs of metastases
3	Tumour size > 5cm and may be attached to surrounding

	muscle or skin. No signs of metastases	
4	Any size tumour, axillary lymph nodes are affected and the cancer has usually metastasised	

Table 1: Staging of invasive breast cancer (27)

Grading of breast cancer refers to the microscopic appearance of the cells; they can be either low-grade or high-grade as explained previously.

Prognosis

Because of biological heterogeneity, only a proportion of patients with a particular type of malignancy benefit from a specific treatment. The difference between predictive and prognostic markers is that predictive

markers show whether a patient is likely to benefit from a specific therapy or not whereas prognostic markers predict the natural course of the disease. The most reliable predictive marker in oncology for the best therapy is the oestrogen receptor (ER).

Research carried out in the early 1970s showed that the ER protein was present in 50-70% of invasive breast cancers and that patients possessing ER-positive tumours responded to endocrine therapy . Thirty years later it was then proven that ER positive tumours were shown to reap benefit from adjuvant hormone therapy. The reasoning behind this will be discussed later on. Factors which contribute to local recurrence are the tumour size, the age of the patient, the resection width and the presence of necroses. In a study carried out by Neuschatz et at, it was concluded that tumours <15mm had no local recurrence regardless of whether they had been irradiated or not. Age is also an important factor as it has been found in the EORTC study that women <40 years had a two fold increase in the recurrence rate as compared to older women.

The reasoning behind focusing my SSM on DCIS and its management strategies is because the treatment has changed dramatically in the past fifteen years, one of these being the introduction of anti-hormonal therapy in particular tamoxifen and aromatase inhibitors. In the next section I will be discussing the changes in the treatment of DCIS and how to decide which patients receive specific hormonal therapy and their advantages and disadvantages.

Method

I searched various databases so I was able to locate articles which were appropriate to my chosen title. I used Scopus as my chosen database. In order to make my search more specific I used words relating to my title and linked them to the operator ‘ AND’. Within my inclusion criteria I reviewed articles published between the years 1990 and 2011 and published in the English language only. After collecting the articles I read the title and abstract and compared them to my chosen title.

Discussion

The current treatment options for early breast cancer depend on the disease characteristics including staging and hormone-receptor status of the tumour. In addition to this, patient characteristics such as age and menopausal status are also taken into account. Treatment strategies for any disease are usually categorised into medical (adjuvant therapy) and surgical procedures. Adjuvant treatment is used to prevent the recurrence of tumours. It involves radiotherapy, chemotherapy, hormone therapy or molecular targeted therapy. In particular the focus of this SSM is on hormonal therapy, and it has been shown that the purpose of this type of therapy is to deprive the tumour cells of the proliferative stimulus provided by oestrogen. Within the breast tissue there are receptors for oestrogen and progesterone which allow the breast to grow or change in response to altering levels of these hormones. Approximately two thirds of women diagnosed with breast cancer have hormone-receptor positive tumours, which tend to grow less aggressively, resulting in a better prognosis (28). The binding of oestrogen to its receptor is blocked by the hormonal therapy in the nucleus; thus is the function of tamoxifen.

The pharmacology of tamoxifen is the inhibition of DNA synthesis and a reduction in oestrogen's effects. It causes cells to remain in the G0 and G1 phase of the cell cycle. It is said to be cytostatic as it doesn't cause cell death but prevents precancerous cells from dividing (29). Tamoxifen competes with oestrogen in the body for binding to oestrogen receptors. The ER/tamoxifen complex needs to block growth factors such as HER2 because they have been shown to appear in tamoxifen resistant cancers.

A study carried out in 1999 by Fisher et al investigated whether lumpectomy, radiation therapy and tamoxifen were more effective than just lumpectomy and radiation therapy alone for patients diagnosed with DCIS. In the previous year before this study, the National Surgical Adjuvant Breast and Bowel Project (NSABP) was prompted to undertake the B-17 study as there was uncertainty about the clinical management of women with small localised DCIS. Until the mid-1980s, mastectomy followed by axillary dissection was the preferred treatment for primary invasive breast cancer and DCIS. The B-17 study reported a significantly improved overall 5-year survival because of the reduced incidence in invasive and non-invasive ipsilateral breast cancers in women who underwent lumpectomy and radiation therapy. The B-24 study was then created after reports of tamoxifen's use in animal studies showed antipromotor and anti-initiator properties As tamoxifen is an antagonist of the oestrogen receptor in breast tissue, it is the standard adjuvant therapy in premenopausal women with positive oestrogen receptor DCIS. It is most effective in premenopausal women as the B-24 study reported that women under the age of 50 had a 38% reduction in ipsilateral-breast tumours compared to women over 50 years who only had a 22% reduction. In

contrast to this, a study carried out by Abe et al found that patients who had ER-negative tumours did not benefit from hormonal therapy in particular tamoxifen. However figure 3 below shows that the progesterone receptor (PR) is a functional marker for active ER as it was investigated that progesterone induced oestrogen by acting on the ER. Therefore it was proposed that those with ER and PR-positive tumours would respond to hormone therapy as opposed to ER-positive PR-negative tumours which would not. Another study supporting this hypothesis was carried out by Bardou et al who proved that the combined expression of ER and PR was superior to ER alone therefore patients who had both ER and PR positive tumours had a better outcome after being treated.

Figure 3 also highlights another important marker HER2 protein, a member of the HER transmembrane receptor tyrosine kinase family which is overexpressed in a quarter of newly diagnosed invasive breast cancers usually resulting from gene amplification. The increased expression causes the enhancement of cell signalling involving certain pathways such as the mitogen-activated protein kinase (MAPK) pathway and the janus kinase/signal transducer and activator of transcriptional (JAK/STAT) pathway, these particular pathways lead to increased cell proliferation, cell motility, cell survival, angiogenesis, invasion and metastasis. It is because of this that HER2 has been investigated as a target for the treatment of breast cancer. Specific antibodies directed against the HER2 ectodomain to inhibit cell lines overexpressing the HER2 have been developed. One specific antibody which has been developed is Trastuzumab, it was found to bind to the HER2 protein and inhibit the growth of breast cancer cells overexpressing HER2. In order

for Trastuzumab to work effectively it is necessary for the overexpression of HER2 to be present to induce tumour regression. Therefore the main clinical use for HER2 is for choosing patients with advanced breast cancer. Many studies carried out highlighted the use of HER2 for predicting the response to hormone therapy, for example a study carried out by Piccart et al concluded that the overexpression of HER2 was associated with resistance after treatment with hormonal therapy in patients with both early and advanced breast cancer. Therefore it has been recommended that HER2 not be used to assess the resistance to hormone therapy as there is insufficient evidence to support this.

Another hormonal therapy which have recently been developed are aromatase inhibitors, it is stated in the BNF journal that these inhibitors are most beneficial in postmenopausal women as opposed to tamoxifen which was more beneficial in premenopausal women (30). Hormone-receptor-positive breast cancer growth is driven by oestrogen. Figure 4 demonstrates their action, which is to decrease plasma oestrogen levels by inhibiting the aromatase enzyme, which drives the synthesis of oestrogen from androgenic substrates such as androstenedione and testosterone. Unlike tamoxifen they do not inhibit oestrogen synthesis and thus should not be prescribed to premenopausal women.

Luteinising hormone releasing agonists (LH-RHa) is another therapy which has recently been developed for postmenopausal patients with advanced breast cancer. However the controversy arises from their role as adjuvant therapy in early stage breast cancer. LH-RHa works by inducing ovarian suppression by decreasing the levels of luteinising hormone and oetradiol by

binding to pituitary LH-RH receptors. A study carried out by Cuzick et al analysed previous trials carried out using LH-RHa. The study showed that by combining LH-RHa and tamoxifen, there was a significant reduction in recurrence and death. However LH-RHa alone did not significantly reduce the risk of recurrence or death. Therefore it is indicated that tamoxifen remain the standard treatment for early ER+ premenopausal breast cancer

Conclusion

In conclusion, breast cancer remains the most common malignancy diagnosed amongst women in the UK. There has been an increased incidence in DCIS due to the development of new diagnostic techniques. In addition to this the treatment for early stage breast cancer has also changed dramatically in the past decade. The introduction of adjuvant hormonal therapy has proven controversial.

The NICE guidelines stipulate that the standard adjuvant hormonal treatment for postmenopausal women with oestrogen-receptor-positive breast cancer is 5 years therapy of tamoxifen (28). Tamoxifen has been shown to have other advantages such as reducing bone fractures in post menopausal women and also reducing serum cholesterol. However there is evidience to suggest that long term use of tamoxifen increases the risk of developing endometrial cancer but for this particular drug the benefits out way the risks. The population of interest which tamoxifen focuses on is premenopausal women diagnosed with early satge DCIS, Fisher et at supported this statement by carrying out a study investigating whether lumpectomy, radiation therapy and tamoxifen were more effective in reducing the risk of recurrence than

lumpectomy and radiation. The results showed a larger reduction in recurrence in those patients being treated with additional tamoxifen.

Trastuzumab another hormonal therapy has been shown to prove beneficial in those women with advanced breast cancer as it suppresses cell growth however as mentioned above there is much controversy over the use of Trastuzumab as a common hormonal therapy. NICE guidelines specify that women suffering from heart problems or high blood pressure should not be treated with this particalar hormone therapy. Lastly LH-RHa inhibitors are still under investigation as to whether they are effective in advanced breast cancer as there are only studies which have been carried combining LH-RHa with other hormonal therapies.

Therefore it is apparent to see that the development of hormonal therapy for DCIS and other forms of breast cancer has shown a positive turn in devleoping more specific targeted treatment for cancers regarding the genetics behind the cause of each different cancer.