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Targeted Therapies in the Management of Breast Cancer

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Abstract

The incidence of cancer is increasing in the United Kingdom. Breast cancer is the most commonly diagnosed cancer among women in the UK with an age standardised rate of 124 per 100000 women. It accounts for almost one-third of all female cases of cancer in the UK and it is the most common form of cancer among women in both developing and developed countries. There are many management options for cancer such as surgery, chemotherapy and radiotherapy. Surgery has been the main treatment option for many solid tumours for several decades. However, research has shown that attacking specific targets within tumours such as receptors, intracellular proteins and genes could result in better clinical outcome. Promising therapeutic targets that have been identified include Raf kinase, Src, HER2, epidermal growth factor receptor and vascular endothelial growth factor receptor. After several decades of intensive research, it appears that we are finally hitting cancer where it hurts. It is very likely that in the near future, more targets for potential therapies would be identified and ultimately, there would be significant reduction in morbidity and mortality from cancers, including breast cancer.

Keywords: Breast cancer; HER2; BRCA genes; Raf kinase; Anti-microtubule; Targeted therapies

Introduction

The incidence of cancer is increasing in the United Kingdom. It has been claimed that more than one-third of the population would develop a malignant disease at some time in their life [1]. Cancer is now the second most common cause of death in the Western world, after cardiovascular disease [1]. In 2008, approximately 309500 people were diagnosed with cancer in the UK, more than half of which are breast, lung, colorectal and prostate [2]. Cancer continues to be a major killer despite the rigorous research and rapid developments in recent years, and the incidence and mortality are likely to increase in the near future. It is expected that the world population would increase to 7.5 billion by 2020 and of this number, approximately 16 million new cancer cases will be diagnosed and 12 million cancer patients will die [3]. Approximately 90-95% of cases can be attributed to environmental factors and lifestyle such as smoking, alcohol, diet and infections [4]. Only 5-10% of all cancer cases can be attributed to genetic defects [4]. There are many management options for cancer such as surgery, chemotherapy and radiotherapy. Surgery has been the main treatment option for many solid tumours for several decades; however research has shown that attacking specific targets within tumours such as receptors, intracellular proteins and genes could result in better clinical outcome. Promising therapeutic targets that have been identified include Raf kinase [5], Src [6], HER2 [7], epidermal growth factor receptor [8] and vascular endothelial growth factor receptor [8]. The aim of this review is to highlight some of the therapeutic targets that have been identified in the treatment of solid tumours, with particular emphasis on breast cancer – the most common cancer in women in the UK.

Breast cancer

Breast cancer is the most commonly diagnosed cancer among women in the UK with an age standardised rate of 124 per 100000 women [2]. It accounts for almost one-third of all female cases of cancer in the UK [2] and it is the most common form of cancer among women in both developing and developed countries [9]. Certain risk factors have been associated with breast cancer. These include age [10], sex, obesity [10], family history of breast cancer [11], late menopause [11], and lack of childbearing and breastfeeding [11]. Like many other cancers, breast cancer is caused by an interaction between the environment and genetic defect. During cell division, DNA is usually copied with several mistakes, which is normally repaired by error-correcting proteins or undergo apoptosis. When there is mutation in these error-correcting mechanisms, the cells begin to divide uncontrollably resulting in tumourigenesis. A number of mutations have been implicated in the pathophysiology of breast cancer. These include mutations in the RAS-RAF-MEK-ERK pathway [12], PI3K/AKT pathway [13], breast cancer susceptibility genes 1 and 2 (BRCA1 and BRCA2) [13] and HER2 [13]. As a result of increasing knowledge about the cellular mechanisms that underlie the genesis of cancer, specific targeted therapies are being developed that block the growth and spread of cancer by interfering with specific molecules that are involved in the growth and progression of tumours. It is thought that this therapeutic strategy may be more effective as it is more specific than treatments such as chemotherapy and radiotherapy which are non-specific and usually have many side effects.

HER2 inhibitors

HER2 belongs to the human epidermal growth factor receptor (HER) family of tyrosine kinases which consists of EGFR (HER1, erbB1), HER2 (erbB2, HER2/neu), HER3 (erbB3) and HER4 (erbB4) [14]. The HER2 gene is located on the long arm of human chromosome 17 and encodes a transmembrane receptor protein with tyrosine kinase activity [15, 16]. Structurally, the receptor is made up of an extracellular ligand-binding domain, transmembrane domain and an intracellular tyrosine kinase catalytic domain [17]. On activation by a ligand, the receptors dimerize and undergo transphosphorylation in order to activate the various intracellular signaling pathways which mediate the proliferation and differentiation of cells [18,19]. HER proteins

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control cell growth, survival, adhesion, migration and differentiation. The cellular mechanism by which HER2 is activated is not entirely understood and it is believed that it is an orphan receptor as there is no known stimulatory ligand for HER2 receptor homodimers [17].

The amplification of HER2 has been implicated in some cancers. Slamon et al. reported that approximately 25-30% of breast cancers have amplification and overexpression of HER2, with such cancers having worse biologic behaviour and prognosis [20]. When alterations of the gene in 189 primary human breast cancers were investigated, HER2/neu oncogene was found to be amplified from 2- to greater than 20-fold in 30% of the tumours [21]. It soon became clear that there is a correlation between the amplification of HER2 and the genesis of human cancers. HER2 amplification or protein overexpression is now used to predict clinical outcome and prognosis in clinical practice. HER2 amplification or protein overexpression has been shown to be a poor predictor of clinical outcome in node-positive patients [17]. It is also associated with increased tumour recurrence and decreased survival.

As a result of the correlation between HER2 amplification and tumourigenesis, it was proposed that inhibiting oncogenic HER2 could be an effective treatment for HER2-driven cancers. This has resulted in the development and use of anti-HER2 antibodies such as trastuzumab (Herceptin) in clinical management. Herceptin is an anti-HER2 monoclonal antibody with an anti-proliferative effect on cells transformed by HER2 overexpression and is an effective treatment for breast cancer [22]. It is thought that herceptin stimulates HER2 endocytosis and removal of HER2 from the cell surface. Sliwkowski et al. claim that trastuzumab induces p27KIP1 – a tumour suppressor protein, and Rb-related protein, p130, which in turn significantly reduces the number of cells undergoing S-phase [23]. Herceptin downmodulates HER2 receptor, inhibits tumour cell growth, reverses cytokine resistance, restores E-cadherin expression levels and reduces vascular endothelial growth factor production [23]. The use of herceptin in clinical practice has resulted in significant reduction in mortality from HER2-overexpressing disease. In an American trial to compare adjuvant chemotherapy with or without concurrent trastuzumab in women with surgically removed HER2-positive breast cancer, trastuzumab therapy was associated with a 33% reduction in the risk of death (P=0.015) [24].

Lapatinib is another drug that has been developed which interrupts the HER2 growth receptor pathway. Lapatinib inhibits the tyrosine kinase activity associated with two oncogenes – EGFR and HER2/neu [25]. Lapatinib works intracellularly by reversibly binding to the cytoplasmic ATP-binding site of the kinase, therefore blocking receptor phosphorylation and activation [26]. This results in the suppression of proliferation pathways of solid tumours, most notably advanced or metastatic breast cancer [27]. In a study by Cameron and associates, the use of lapatinib in combination with capecitabine in women with HER2-positive, locally advanced and metastatic breast cancer resulted in improved overall survival and prolonged time to progression [28].

In view of the success of HER2 targeting agents, it is very likely that in the coming decade, a second generation of HER2-targeting agents would be introduced into clinical testing in an attempt to treat HER2-driven cancers via inactivation of HER2. With a better understanding of the cellular mechanisms by which HER2 is activated, more novel therapies are likely to be developed with different mechanisms of action.

BRCA genes

Breast cancer susceptibility genes 1 and 2 (BRCA1 and BRCA2) are tumour suppressor genes. In normal cells, BRCA 1 and BRCA 2 help to ensure the stability of the cell's genetic material and prevent uncontrolled cell growth [29]. Mutation of BRCA1 and BRCA2 gene has been shown to be associated with an increased risk of developing breast cancer. BRCA1 and BRCA2 both interact with RAD51 – a protein – in the repair of DNA double-strand breaks [30]. When BRCA1 or BRCA2 gene becomes defective, damaged DNAs begin to accumulate as the repair mechanism is lost, resulting in uncontrolled division and tumourigenesis. In a study by Risch and colleagues, they claim that the estimated cumulative incidence of breast cancer to age 80 years among women carrying the BRCA1 and BRCA2 mutations was 90% and 41% respectively [31]. It is therefore evident that mutation in BRCA1 or BRCA2 gene increases the risk of developing breast cancer. Hence it has been suggested that specifically targeting the mechanism for single-strand DNA repair on which the tumour cells depend could offer a therapeutic strategy in inhibiting tumour growth and progression since the double-strand DNA repair mechanism is already damaged. This resulted in the development of PARP inhibitors. Poly ADP ribose polymerase (PARP) is a protein that plays a crucial role in the repairing of single-strand breaks, particularly PARP1 which acts as a sensor of DNA damage and initiate base excision repair pathway [32]. In a phase 1 trial by Fong and colleagues, they administered olaparib (a PARP inhibitor) to patients who carry the BRCA1 or BRCA2 mutation and reported anti-tumour activity in all the mutation carriers [33]. Although no lethal adverse effects were reported, it is important to study the potential long-term adverse effects of PARP inhibitors. This is because PARP1 has several other important roles including restarting stalled replication, inhibiting non-homologous end-joining repair, regulating transcription, initiating a unique cell death pathway and modulating cellular biogenesis [34]. Hence inhibiting PARP may significantly affect these processes, which would be detrimental to cells.

Although there may be potential drawbacks to the use of PARP inhibitors in the treatment of breast cancers, it would be interesting to see the results of the Phases II and III trials as there is a potential that clinical benefits would be produced in BRCA-deficient tumours.

Rapidly Accelerated Fibrosarcoma (Raf) kinase inhibitors

Raf kinases are a family of three serine/threonine-specific protein kinases that are related to retroviral oncogenes and were discovered in 1983 [35]. Members of the RAF family include A-RAF, B-RAF and C-RAF (formerly known as RAF-1). RAF kinases participate in the RAS-RAF-MEK-ERK signal transduction cascade, which is sometimes denoted as the mitogen-activated protein kinase (MAPK) cascade [35]. Activation of RAF kinase activity is a multistage process requiring interaction with RAS-GTP. The RAF kinases have restricted substrate specificity and catalyze phosphorylation and activation of MEK1 and MEK2 [36]. MEK1/2, which are dual specificity protein kinases, mediate the phosphorylation of tyrosine before threonine in ERK1 or ERK2 (**E**xtracellular-signal **R**egulated protein **K**inase) – their only substrates [36]. The phosphorylation activates ERK1/2, which are protein-serine/threonine kinases [36]. Unlike RAF and MEK1/2 that have narrow substrate specificity, ERK1 and ERK2 have many substrates. This cascade is important in the regulation of several processes including apoptosis, cell cycle progression, differentiation, proliferation and transformation to the cancerous state [36].

The physiological regulation of RAF kinases is complex and involves several steps such as protein-protein interactions, phosphorylation,

dephosphorylation and conformational changes [37]. The activation of oncogenic mutation within the upstream RAS gene implicated in tumourigenesis can result in constitutive activation of downstream RAF-1 [38]. This then induces DNA synthesis resulting in malignant transformation, loss of growth factor dependence and contact inhibition, increased cell survival and invasion/metastasis, all of which are pathognomonic features of cancerous cells. It has been claimed that oncogenic ras mutations occur in as many as 90% of pancreatic and half of thyroid and colorectal carcinomas [38]. RAS mutations have also been implicated in acute myeloid leukemia, melanoma and kidney tumours [38,39]. The activation of b-raf mutations also occur at a high frequency in certain human cancers, with the most common variant being b-raf V600E present in 63% of melanomas [40], 40% of sporadic colorectal tumours [41] and 38%-50% of papillary thyroid carcinomas [42,43]. Mutations in k-ras and b-raf have also been implicated in human breast cancer cell lines. Although initially thought to be rare, k-ras mutation was noted in 13% of breast cancer cell lines studied by Hollestelle et al. while 25% of the breast cancer lines were found to have mutational activation of RAS signaling pathways [44].

There has been development of therapies targeting the RAS-RAF-MEK-ERK pathway with the aim of downregulating the cellular activities, therefore inhibiting tumour cell growth. Sorafenib has been developed to inhibit RAF isoforms. It is a synthetic, orally available bi-aryl urea and is the most promising of the RAF kinase inhibitors in clinical development [45]. In cellular assays, sorafenib inhibits the phosphorylation of ERK1/2 (pERK) and MEK 1/2 (pMEK), thus supporting its RAF inhibitory effects in human cells [46,47]. It has also been demonstrated that sorafenib reduces pERK levels in tumour cell lines with oncogenic k-ras or b-raf genes [46]. The inhibitory effects of Sorafenib on RAF isoforms in vivo is also supported by preclinical studies demonstrating its dose-dependent growth inhibitory effect on human colon and breast tumour xenografts containing *k-ras* or *b-raf* mutations [46]. Sorafenib has been shown to have activity against ovarian, pancreatic, breast and melanoma tumour xenograft models [46]. In a study by Gradishar et al. it was observed that sorafenib, in combination with paclitaxel, resulted in significant improvement in survival in patients with HER2-negative, locally recurrent or metastatic breast cancer [48].

It would be interesting to study the effectiveness of each of the targeting agents discussed above in relation to the genotype of patients. It may well be demonstrated, for example, that patients who are HER2-positive have better prognosis when treated with Trastuzumab or Lapatinib while patients who are HER2-negative have improved clinical outcome when treated with Sorafenib, rather than Trastuzumab.

Anti-microtubule agents

Anti-microtubule agents are drugs that stop mitosis, therefore blocking cell growth. Microtubules are cellular structures that help to move chromosomes during mitosis and it is these structures that anti-microtubule agents interfere with. There are a number of anti-microtubule agents such as colchicine and the vinca alkaloids. However, the anti-microtubule agent which is of interest to oncologists is paclitaxel. Unlike typical anti-microtubule agents which induce depolymerization of microtubules, paclitaxel induces tubulin polymerization and forms extremely stable and nonfunctional microtubules [49]. It blocks cells in the G2/M phase of the cell cycle and such cells are unable to form a normal mitotic apparatus [50]. Studies have shown that paclitaxel is active in the treatment of metastatic breast cancer as a first-line therapy [51,52]. In a study in Texas, researchers reported that when paclitaxel was administered to 25 patients with metastatic breast cancer at a dose of 250 mg/m^2 every 21 days, there was an objective response rate of 56% [53]. In a similar study in New York, the objective response rate was 62%, with responses observed in all sites of metastatic disease [54]. However, paclitaxel has serious side effects such as neutropenia, peripheral neuropathy and neurotoxicity. It is therefore important to monitor patients who are being treated with paclitaxel closely. Vinorelbine is another anti-mitotic agent being investigated in the treatment of metastatic breast cancer and preliminary results seem promising [55], although its action is distinct from that of paclitaxel. Vinorelbine binds to tubulin and inhibits microtubule formation resulting in the disruption of mitotic spindle formation, thereby arresting the cell at metaphase.

While antimicrotubule agents appear to be extremely active against metastatic breast cancer, there should be research into overcoming the toxicities associated with these agents. There should also be more research into the combination of various anti-microtubule agents, which may reveal increased efficacy.

Conclusion

Specific targeted therapies have been discussed with particular emphasis on breast cancer. Some of these therapies are still undergoing clinical trials and it would be interesting to see the results of these trials. It is paramount that researchers ascertain the optimal dosing of these targeting agents in order to achieve maximal anti-tumour effect with minimal or tolerable toxicity. After several decades of intensive research, it appears that we are finally hitting cancer where it hurts. It is very likely that in the near future, more targets for potential therapies would be identified and ultimately, there would be significant reduction in morbidity and mortality from cancers.

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