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Literature review on targeted therapies in management of solid tumours

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Abstract

Purpose: To depict the emergence of targeted therapies that have led to distinguished breakthrough in the management of cancer.

Methods: The literature was systematically reviewed, based on their evolution and their use with understanding on the adverse effects.

Results: Cancer genomics and model systems have enabled new therapeutic strategies. Targeted therapy is a novel cancer treatment that targets the specific molecular targets associated with cancer, where as chemotherapy drugs act on rapidly dividing normal and cancer cells. Most types of targeted therapies are designed to interact with the specific target. Targeted therapies can block or turn off signals thus control growth, division of cancer cells. Most targeted therapies are either small-molecule drugs or monoclonal antibodies. Targeted therapies are the cornerstone of precision medicine that uses information about the genes and protein. This review will discuss various targeted therapies in management of solid tumors.

Keywords: Targeted therapy for solid tumours; Targeted therapy drugs; Molecular Targeted therapy; Precession Cancer treatment; Molecular Medicine for cancer

1. Introduction

Chemotherapy for cancer treatment has been one of the major medical advances in the last few decades. However, the drugs used for chemotherapy have a narrow therapeutic index, with varied toxicities ranging from nausea, Bone marrow suppression. With the evolving landscape of medical oncology the focus has shifted away from non-specific cytotoxic treatments strategies toward therapeutic paradigms more characteristic of precision medicine by using Targeted therapies.

Targeted therapy uses drugs which are directed against cancer-specific molecules and signalling pathways and thus has more limited nonspecific toxicities.

According to their mechanism of action and prevalence, targeted therapeutics can be broadly classified into:

- Monoclonal antibodies
- Small molecule inhibitors of various, mostly, protein functions

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Tyrosine kinases are an especially important target because they play an important role in the modulation of growth factor signalling. The first striking examples of clinically beneficial rational therapies using a small molecule acting as kinase inhibitor were observed in a hematological malignancy. When applying precision medicine, the goal is to tailor diagnosis and treatment to each patient's individual biologic profile, while minimizing exposure to unnecessary or ineffective therapies. These developments have shifted precision oncology to the forefront of cancer treatment strategies. Here, we review the implementation of precision oncology using targeted therapies in various solid tumors. We also discuss various toxicities associated with targeted therapies.

Objective

The following review will focus on targeted inhibitors which are of proven clinical value in the treatment of solid tumours.

1.1 Design

Systematic literature review.

1.2 Data source

Electronic search of research articles, review papers and RCT's from PubMed, science direct, Web of Science, Mendeley and Medline.

2. Discussion

Extensive investigations of carcinogenesis and tumor characterization have identified various deregulations within tumors and their microenvironments and have helped steer the direction of drug development in cancer. The two main types of targeted therapy are monoclonal antibodies and small molecule inhibitors. A primary goal of targeted therapies is to fight cancer cells with more precision and potentially fewer side effects. Target engagement can be achieved through several modalities that modulate or interact with cell surface receptors (monoclonal antibodies), intracellular cascade pathways and signalling (small molecule tyrosine kinase inhibitors) or micro-environment effects related to tumor vasculature or hypoxia. Aberrations in various cellular signalling pathways are instrumental in regulating cellular metabolism, tumor development, growth, proliferation, metastasis, and cytoskeletal reorganization. The use of targeted therapy has markedly changed outcomes for some diseases. Imatinib has had a dramatic effect on chronic myeloid leukaemia, sunitinib, and trastuzumab have revolutionized the treatment of renal cell carcinoma, and breast cancer, respectively.

3. Breast

Aiming at hormone receptors that are present on some breast cancer cells have been essentially the starting point of targeted anti cancer therapy. By binding to the estrogen receptor on cell surfaces in a competitive manner, tamoxifen became the mainstay of endocrine intervention in all breast cancer settings and is still used today as part of the standard of care. The development of aromatase inhibitors, which, by inhibiting aromatase the enzyme that catalyzes the conversion of androgens to estrogens can decrease circulating estrogen to nearly zero in postmenopausal women who already lack ovarian estrogen production, became the standard of care in postmenopausal women.

Overexpression of HER2, which occurs in approximately 20% of breast cancers and largely is because of a specific gene copy number amplification, results in a hyper proliferative cancer cell and poor prognosis. This plus emerging evidence that cancer cells can become oncogenically addicted which means that a single aberrant oncogene becomes such a driving force for growth and proliferation that other usually relevant pathways atrophy makes HER2 a highly attractive therapeutic target.

Aberrant cellular proliferation due to deregulation of the cyclin-dependent kinase (CDK) retinoblastoma (Rb)-pathway occurs in several cancers. Selective inhibition of CDK4/6 is an attractive target, particularly in hormone-receptor positive (HR+) metastatic breast cancer (MBC), where it has transformed the treatment of these cancers in recent years. Three CDK4/6 inhibitors, palbociclib, ribociclib, and abemaciclib, have been approved for the treatment of HR+, HER2 negative (HER2-) MBC.

BRCA1 and BRCA2 (Breast Cancer) proteins are involved in homologous recombination repair (HRR), which requires a homologous chromosome or sister chromatid as a template to faithfully repair DNA double-strand breaks. Poly-ADP-ribose polymerase 1 (PARP-1) and PARP-2 are DNA damage sensors that are most active during S-phase of the cell cycle

and have roles in DNA repair. The small-molecule NAD+ mimetics, olaparib, niraparib, rucaparib, veliparib, and talazoparib, inhibit the catalytic activity of PARP-1 and PARP-2.

4. Tamoxifen

Tamoxifen is a Non-steroidal antiestrogen having weak estrogen agonist effects. It competes with estrogen for binding to ERs. Binding of tamoxifen to ER leads to ER dimerization. The tamoxifen-bound ER dimer is transported to the nucleus, where it binds to DNA sequences. This interaction results in inhibition of critical transcriptional processes and signal transduction pathways that are required for cellular growth and proliferation[1].

It is indicated in ER positive breast cancer patients following resection, adjuvant chemotherapy and radiation therapy and in metastatic breast cancer in women and men. It is also indicated as adjuvant therapy in women with ductal carcinoma in situ (DCIS) after surgical resection and radiation therapy.

5. Letrozole

This drug belongs to the class of aromatase inhibitors. Aromatase, an enzyme of the cytochrome P-450 super family and the product of the CYP19 gene, is expressed in several tissues, including subcutaneous fat, liver, muscle, brain, normal breast tissues, and mammary adenocarcinoma. It is responsible for the conversion of the adrenal androgen substrate androstenedione to estrogen in peripheral tissues, the predominant source of estrogen in postmenopausal women. Aromatase inhibitors (AIs) can reduce estrogen production by more than 90%. It is indicated as first-line treatment of postmenopausal women with hormone receptor positive or hormone-receptor unknown locally advanced or metastatic breast cancer. It is indicated as second-line treatment of postmenopausal women with advanced breast cancer after progression on anti-estrogen therapy. FDA has approved it as an extended adjuvant treatment of early-stage breast cancer in postmenopausal women who have received 5 years of adjuvant tamoxifen therapy.

6. Trastuzumab

Trastuzumab are the human monoclonal IgG antibodies which selectively targets HER2, a human epidermal growth factor receptor (EGFR). Trastuzumab inhibits the growth of tumour cells that overexpress HER2 on the surface of breast, gastric, ovarian, lung, and prostate cancer cells. Mechanisms involved include: decreasing VEGF production, activating antibody-dependent cell-mediated cytotoxicity, G0/G1 cell cycle cytotoxicity, and inhibiting intracellular signalling pathways[2]. Trastuzumab is indicated for breast cancer patients with a proven amplification of the HER-2 oncogene or overexpression of the HER-2 protein in the tumor. Overexpression of HER-2 or amplification of HER-2 is associated with adverse disease prognosis and shorter overall and disease-free survival time [3]. Trastuzumab is indicated in HER-2+ early breast cancer:

- As adjuvant treatment and
- As neoadjuvant treatment.

Trastuzumab is also indicated in HER-2+ metastatic adenocarcinoma of the stomach or gastroesophageal junction in combination with capecitabine or 5-fluorouracil and cisplatin in patients who have not received prior anticancer therapy for their metastatic disease.

7. Pertuzumab

Pertuzumab is a humanized monoclonal antibody binds to a different HER 2 epitope than trastuzumab and leads to inhibition of hetero-diamerisation of HER2 with other HER2 family members like EGFR, HER 3 AND HER4. This inhibition of heterodimerization leads to inhibition of downstream signalling via intracellular pathways like MAPkinase, PI3K and initiation of cell apoptosis. Indicated in combination with trastuzumab for breast cancer patients with HER2 neu positive/ locally advanced/ inflammatory or early stage breast cancer at high risk of recurrence. For HER 2 neu positive, metastatic breast cancer patients who have not received prior anti HER2 therapy, pertuzumab is used in combination of trastuzumab and docetaxel as 3 weekly regimen [4,5,6,7,8]

8. Palbociclib

Palbociclib inhibits cyclin-dependent kinases 4/6, resulting in a blockade of phosphorylation of the retinoblastoma protein, which hinders the activation of transcription factors involved in S-phase entry, thereby arresting cell cycle progression at the G1 phase 3.

Palbociclib is indicated in combination with an aromatase inhibitor as initial endocrine therapy (ET) or with fulvestrant for patients with disease progression following ET for hormone receptor positive, human epidermal growth factor receptor 2 negative ABC or metastatic breast cancer. The efficacy and safety of palbociclib in combination with ET was established in three randomized trials (PALOMA-1, 2, and 3).

9. Ribociclib

Ribociclib was approved in March 2017 for first-line treatment of HR+/HER2− advanced breast cancer in postmenopausal women, based on the results of the phase III MONALEESA-2 study. In this study, treatment-naive patients with HR+/HER2− advanced breast cancer received letrozole with ribociclib or placebo[9]. Prior AI therapy was allowed if it had been discontinued 12 months before enrolment. At the 18-month follow-up, median PFS had not been reached in the ribociclib-treated arm, compared with a median PFS of 14.7 months in the placebo group (HR, 0.56; 95% CI, 0.43–0.72; P< .001). Updated analysis showed a median PFS of 25.3 months in the ribociclib group vs 16.0 months in the placebo group.

9.1 Everolimus

Everolimus is an M-TOR inhibitor, which is approved by FDA, in combination with aromatase inhibitors for treatment of estrogen receptor positive (ER+) breast cancer patients who have become resistant to hormonal-based therapies and have progressed[10].

9.2 Ovarian Cancer

Greater understanding of tumour biology of OC has led to the development of targeted anticancer medications that have the ability to improve tumour responses to platinum based chemotherapy, thereby alleviating some of the limitations of the latter. The most advanced agents in this regard are bevacizumab, an intravenously-administered vascular endothelial growth factor inhibitor, and olaparib, a first-in-class, orally-active, small molecule, poly (ADP-ribose) polymerase (PARP) inhibitor

9.3 Olaparib

Olaparib is a first-in-class, orally-active, small molecule, poly (ADP-ribose) polymerase inhibitor that induces synthetic lethality in homozygous BRCA-deficient cells. Olaparib is indicated as monotherapy for the maintenance treatment of adult patients with platinum-sensitive, relapsed, BRCA-mutated (germline and/or somatic), high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to platinum-based chemotherapy[11]. Single-agent olaparib was generally well tolerated, with the majority of adverse events being of mild to moderate severity and not requiring interruption of treatment. Fatigue, anaemia and neutropenia were the most frequently reported severe (grade ≥3) adverse events.

9.4 Lung cancer

In recent years, there has been a major paradigm shift in the management of non-small cell lung cancer (NSCLC). NSCLC should now be further sub-classified by histology and driver mutation if one is known or present. Up to 60% of lung adenocarcinoma and up to 50-80% of SCC have a known oncogenic driver mutation9 ultimately these lead to uncontrolled growth, proliferation and survival. For NSCLC, mutations of the epidermal growth factor receptor (EGFR) and on the abnormal fusion of the anaplastic lymphoma kinase (ALK) are being inhibited successfully with EGFR tyrosine kinase inhibitors (TKI) and crizotinib respectively.

10. Gefitinib and Erlotinib

Gefitinib and Erlotinib are potent and selective small molecule inhibitors of the EGFR tyrosine kinase, resulting in inhibition of EGFR autophosphorylation and inhibition of EGFR signalling. Inhibition of the EGFR tyrosine kinase results in inhibition of critical mitogenic and anti-apoptotic signals involved in proliferation, growth, metastasis, angiogenesis,

and response to chemotherapy and/or radiation therapy[12]. Erlotinib and Gefitinib are approved drugs for the treatment of patients with locally advanced or metastatic non-small cell lung cancer harbouring EGFR mutation.

10.1 Crizotinib

Crizotinib is an inhibitor of receptor tyrosine kinases including ALK and Hepatocyte Growth Factor Receptor (HGFR, c-Met). Translocations can affect the ALK gene resulting in the expression of oncogenic fusion proteins. The formation of ALK fusion proteins can contribute to increased cell proliferation and survival in tumors expressing these proteins[13]. Crizotinib demonstrates concentration-dependent inhibition of ALK. It is indicated in locally advanced or metastatic non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (ALK) positive. A dose of 250 mg twice daily orally, continue treatment until no longer clinically beneficial or development of unacceptable toxicity.

10.2 Dabrafenib

About 3% of patients with NSCLC harbor a BRAF V600E mutation. In June 2017, the FDA approved the combination of dabrafenib/trametinib for treatment of patients with BRAF V600E-positive advanced or metastatic NSCLC. Dabrafenib targets BRAF and Trametinib targets MEK1/2.This regimen has demonstrated response rates of more than 50% with a progression-free survival of 9 to 12 months[14].

10.3 Gastrointestinal stromal tumours

GISTs express the cell surface transmembrane receptor tyrosine kinase KIT, which often is mutated, most frequently in exon 11 encoding the intracellular juxtamembrane region and platelet-derived growth factor receptor α (PDGFR-A) proto-oncogenes. Expression of KIT protein is seen in almost all GISTs, and is therefore regarded as one of the key diagnostic markers. Constitutive activation of the c-kit gene is thought to contribute to uncontrolled tumour growth and resistance to apoptosis.

Imatinib is a small-molecule tyrosine kinase inhibitor that effectively blocks both KIT and PDGFR-A signalling. In advanced GIST imatinib has been demonstrated to improve median overall survival dramatically from approximately 20 months to nearly 5 years. However, not all activating mutations confer the same degree of sensitivity to imatinib therapy[15]. KIT exon 11 mutations are associated with increased benefit compared with exon 9 mutation or where there is no identifiable mutation.

10.3.1 Colorectal cancer

The addition of targeted therapies has improved OS in mCRC to between 20 and 29 months. The anti-epidermal growth factor receptor (EGFR) monoclonal antibodies cetuximab and panitumumab, the anti-vascular endothelial growth factor (VEGF) monoclonal antibody bevacizumab and the anti-VEGF receptor 2 (VEGFR2) monoclonal antibody ramucirumab, the recombinant fusion protein ziv aflibercept, and the oral multikinase inhibitor regorafenib About 40 percent of patients with colorectal cancer have tumours with mutant KRAS. When KRAS is mutated, it does not respond to the usual EGFR-mediated signals and unrestricted growth can occur.

10.4 Bevacizumab

Bevacizumab is a recombinant humanized monoclonal antibody directed against the vascular endothelial growth factor (VEGF). It binds to all isoforms of VEGF-A. VEGF is a pro-angiogenic growth factor that is overexpressed in a wide range of solid human cancers, including colorectal cancer. Binding of VEGF prevents its subsequent interaction with VEGF receptors on the surface of endothelial cells and tumors, and in so doing, results in inhibition of VEGFR-signaling. It is indicated in metastatic colorectal cancer for use in combination with any intravenous 5-fluorouracil-based chemotherapy in first-line therapy[16].

10.4.1 Renal cell carcinoma

Several small-molecule protein kinase inhibitors that block angiogenesis, Akt/mTOR and/or Ras/Raf pathways (including sunitinib, sorafenib, pazopanib and everolimus) now have confirmed efficacy in the setting of advanced disease.There has been interest in the use of neoadjuvant TKI therapy to downsize larger tumours and allow more patients to undergo nephron-sparing surgery.

10.5 Sunitinib Malate

Sunitinib (from Pfizer) is an oral multi-kinase inhibitor; it inhibits multiple receptor tyrosine kinases (RTKs), some of which are implicated in tumour growth, pathologic angiogenesis, and metastatic progression of cancer. Inhibitory

activity was detected against platelet derived growth factor receptor (PDGF- and PDGFR-), vascular endothelial growth factor receptors (VEGFR1, VEGFR2 and VEGFR3), stem cell factor receptor (KIT), Fms-like tyrosine kinase-3 (FLT3), colony stimulating factor receptor type 1 (CSF-1R), and glial cell line derived neurotrophic factor receptor (RET)[17]. Sunitinib is available as oral capsules of 12.5, 25, and 50 mg. The recommended dose is 50 mg once daily for 4 weeks followed by a 2-week rest. Dosage reductions in 12.5 mg increments are recommended for intolerable sunitinib-related toxicities.

10.5.1 Oesophagogastric cancer

Biomarkers of interest are now beginning to emerge In HER-2-positive gastric cancer, following the success of Trastuzumab for Gastric cancer (ToGA) trial in advanced disease, there are now several case reports of patients receiving chemotherapy plus trastuzumab.

10.6 Ramucirumab

Vascular endothelial growth factor receptor 2 (VEGFR2) and its ligands are important mediators of angiogenesis and contribute to gastric cancer pathogenesis. Ramucirumab is a human monoclonal antibody (IgG1) against vascular endothelial growth factor receptor 2 (VEGFR2), a type II trans-membrane tyrosine kinase receptor expressed on endothelial cells. By binding to VEGFR2, ramucirumab prevents binding of its ligands (VEGF-A, VEGF-C, and VEGF-D), thereby preventing VEGF-stimulated receptor phosphorylation and downstream ligand-induced proliferation, permeability, and migration of human endothelial cells. VEGFR stimulation also mediates downstream signalling required for angiogenesis and is postulated to be heavily involved in cancer progression, making it a highly likely drug target. In contrast to other agents directed against VEGFR-2, ramucirumab binds a specific epitope on the extracellular domain of VEGFR-2, thereby blocking all VEGF ligands from binding to it[18]. It is indicated as a single agent or in combination with paclitaxel, for treatment of advanced or metastatic gastric or gastro-esophageal junction adenocarcinoma with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy.

10.6.1 Hepatocellular carcinoma

In early-stage disease amenable to surgery, partial liver resection represents the optimal surgical approach but this requires adequate functional liver reserve. Owing to underlying cirrhosis and liver dysfunction in the majority of patients with HCC, an appropriate oncological resection may not be feasible. Some patients harbouring small tumours may be candidates for liver transplantation. Sorafenib is a TKI which acts to inhibit a number of different protein kinases, notably vascular endothelial growth factor receptor (VEGFR), PDGFR, and Raf.

11. Sorafenib

Sorafenib is a kinase inhibitor that decreases tumour cell proliferation through inhibition of multiple intracellular (c-RAF, BRAF and mutant BRAF) and cell surface kinases (KIT, FLT-3, RET, VEGFR-1, VEGFR- 2, VEGFR-3, and PDGFR-ß). Sorafenib bioavailability is reduced by food up to 30 % compared to administration in the fasted state[19]. It is therefore recommended to administer sorafenib without food. Sorafenib is approved for the treatment of patients with unresectable hepatocellular carcinoma (HCC)and for the treatment of patients with advanced renal cell carcinoma. For patients with advanced RCC, the median progression free survival (PFS) time was 5.5 months for patients treated with sorafenib, compared with 2.8 months for those treated with placebo ($p < .01$). Partial responses were reported in 10% of patients treated with sorafenib.

11.1 Lenvatinib

Lenvatinib is a receptor tyrosine kinase (RTK) inhibitor that inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4). Lenvatinib also inhibits other RTKs that have been implicated in pathogenic angiogenesis, tumor growth, and cancer progression in addition to their normal cellular functions, including fibroblast growth factor (FGF) receptors FGFR1, 2, 3, and 4; the platelet derived growth factor receptor alpha (PDGFRα), KIT, and RET[20]. Lenvatinib is indicated in unresectable hepatocellular carcinoma in the first line. The recommended dose is 12mg for patients weighing more than 12 kgs and 8 mg for those who are under 60kgs. Continue treatment till unacceptable toxicity or disease progression.

11.2 Head and Neck Squamous cell carcinoma

The HER (erbB) family of transmembrane receptor tyrosine kinases is one of the cytostatic targets in tumor cell growth and survival. This family, which includes epidermal growth factor receptor (EGFR), plays a pivotal role in normal cell

growth, lineage determination, repair, and functional differentiation.Overexpression of EGFR is recognized in more than 80% of squamous cell cancers, and this overexpression is associated with a poor prognosis.

12. Cetuximab

Cetuximab is a recombinant, chimeric monoclonal antibody (murine anti-EGFR antibody with human IgG1 heavy and kappa light chain constant regions) that binds specifically to the extracellular domain of the human epidermal growth factor receptor (EGFR) both normal and tumour cells, and competitively inhibits the binding of epidermal growth factor(EGF) and other ligands, such as transforming growth factor– alpha. Binding to the EGFR blocks phosphorylation and activation of receptor-associated kinases, resulting, amongst others, in inhibition of cell growth, induction of apoptosis, decreased matrix metalloproteinase and vascular endothelial growth factor production[21]. It is indicated in locally or regionally advanced squamous cell carcinoma of the head and neck in combination with radiation therapy. It is indicated in recurrent locoregional disease or metastatic squamous cell carcinoma of the head and neck in combination with platinum-based therapy with fluorouracil.

13. Thyroid cancer

The treatment of advanced thyroid cancer has undergone rapid evolution in the last decade, with multiple kinase inhibitor drugs. FDA–approved drugs are antiangiogenic multikinase inhibitors—vandetanib, cabozantinib, sorafenib, lenvatinib—there are two FDA indications that are mutation specific—dabrafenib/trametinib for BRAF-mutated anaplastic thyroid cancer and larotrectinib for NTRK-fusion thyroid cancer. Cabozantinib is an oral multikinase inhibitor targeting MET in addition to VEGFR and is approved for medullary thyroid cancer.

13.1 Cabozantinib

Cabozantinib inhibits the activity of c-met, vascular endothelial growth factor receptor (vegfr), and other tyrosine kinases, thereby leading to reduced tumor angiogenesis, motility and invasiveness. Hgf, hepatocyte growth factor; hif-1a, hypoxia-inducible factor 1-a. The use of cabozantinib (cabometyx) in patients with radioiodine-refractory differentiated thyroid cancer (dtc) was found to significantly prolong progression-free survival (pfs) and could possibly be a new treatment option for a population of patients with no available standard of care, according to the results of the phase 3 cosmic-311 trial (nct03690388)[22].

13.2 Clinical Response

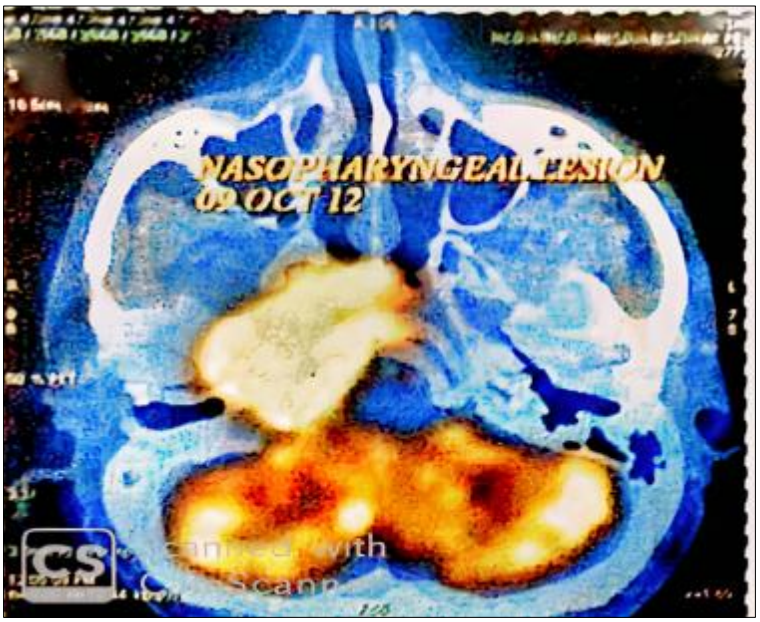

Figure 1 Ca nasopharynx initial disease status on PET-CT

The following examples are of some of the patients who were treated at our centre. Complete morphological and metabolic response seen in a patient treated with Chemoradiation and cetuximab (Fig 1, 2). Excellent response seen in a HNSCC patient treated with Gefitinib (Fig 3, 4). Total resolution of disease involving skin in a HER 2 positive carcinoma

breast patient treated with Trastuzumab (Fig 5, 6). Excellent response seen in a HNSCC patient treated with Gefitinib for the residual disease after chemoradiation (Fig 7, 8).

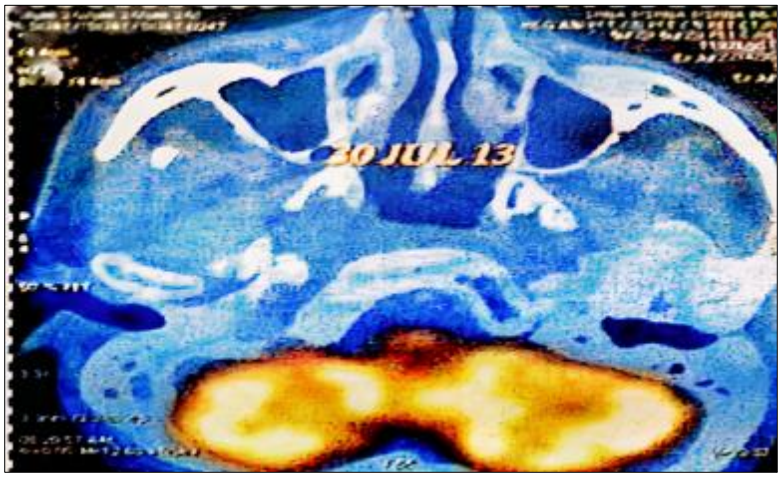

Figure 2 Complete morphological and metabolic response after cetuximab in same patient on PET-CT

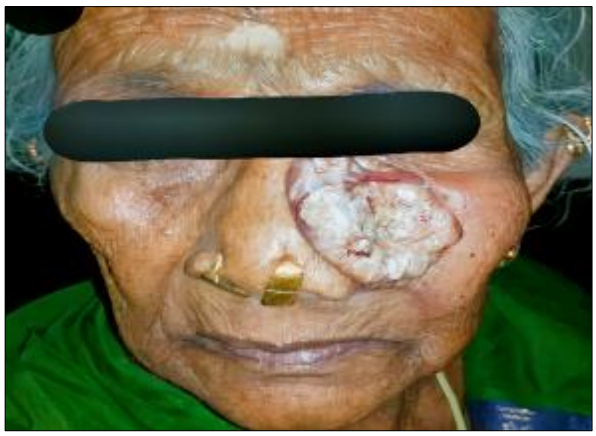

Figure 3 HNSCC patient Initial disease status

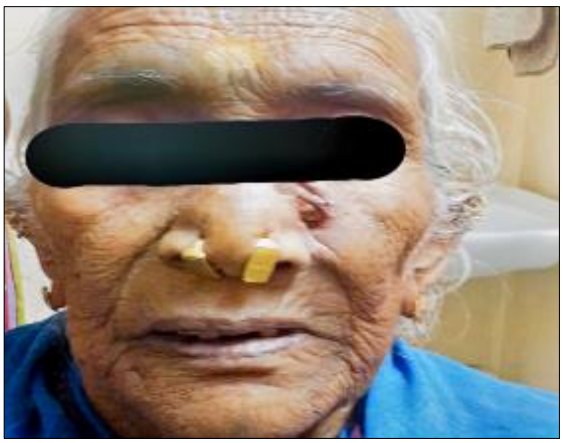

Figure 4 Complete clinical response in same patient after treatment with Gefitinib

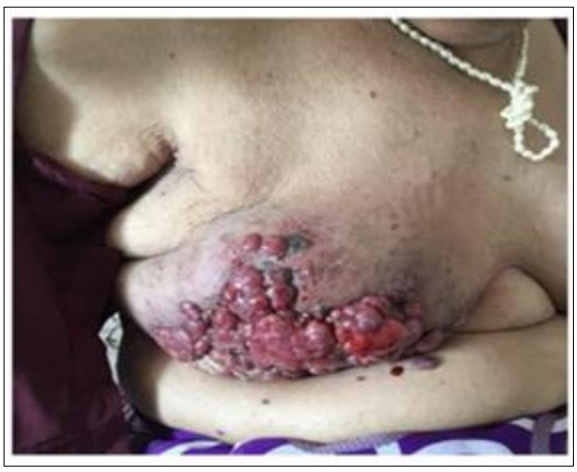

Figure 5 Initial disease status involving skin in a HER 2 positive carcinoma breast

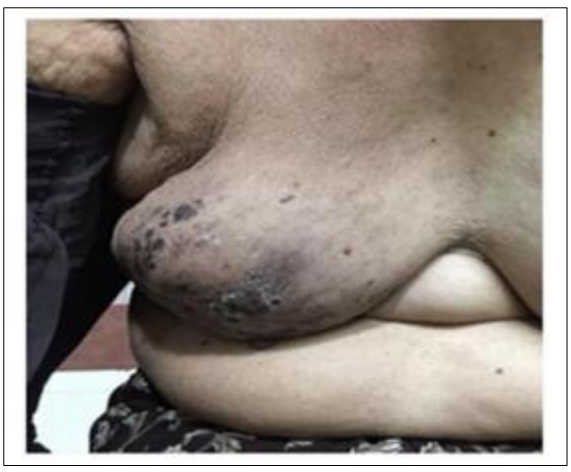

Figure 6 Total resolution of disease in same patient after Trastuzumab

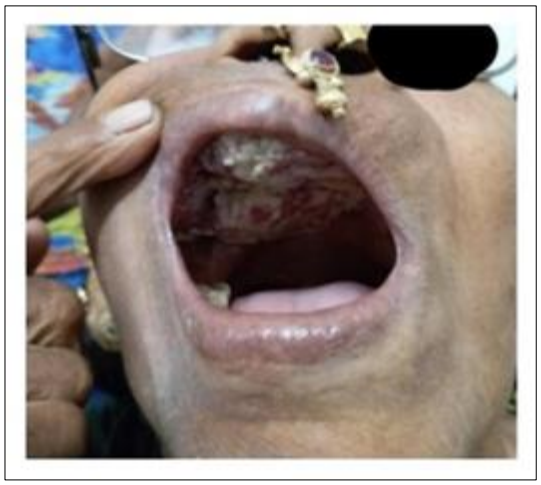

Figure 7 HNSCC patient with residual disease

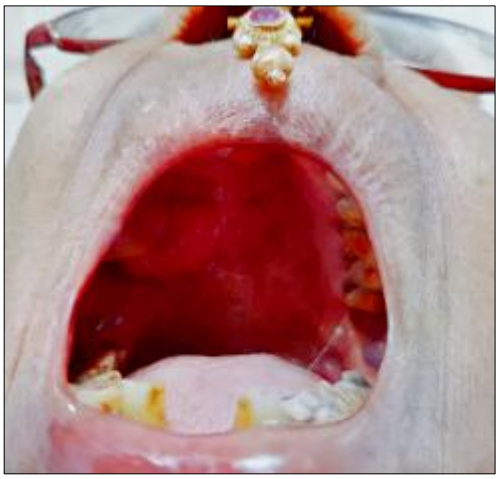

Figure 8 Complete clinical response in same patient treated with Gefitinib for the residual disease

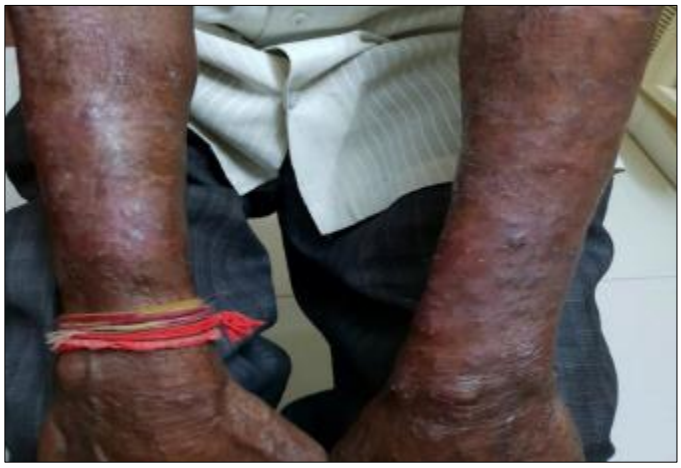

Figure 9 Papulopustular eruption ion hands after treatment with anti-EGFR agents

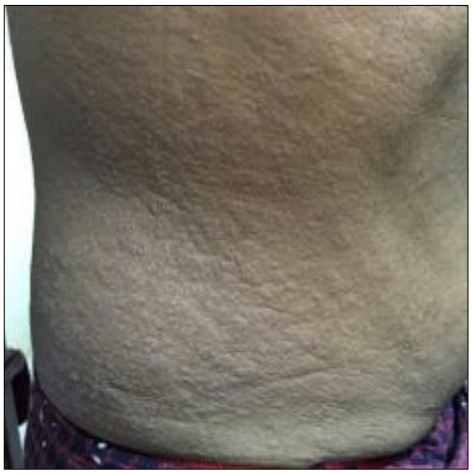

Figure 10 Papulopustular eruption on trunk after treatment with anti-EGFR agents

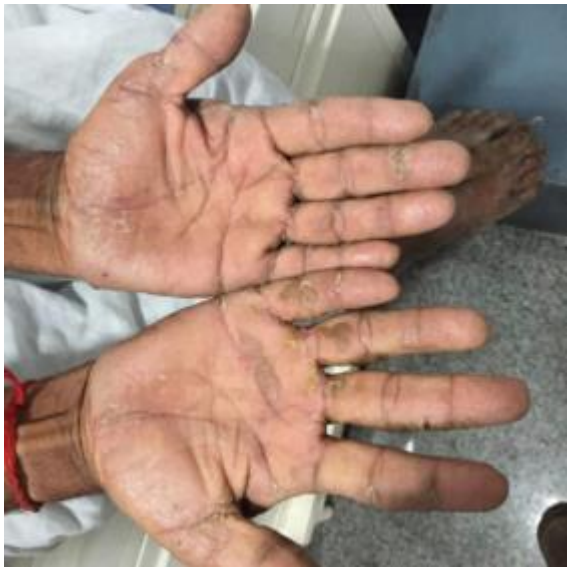

Figure 11 Acral reactions with capecitabine

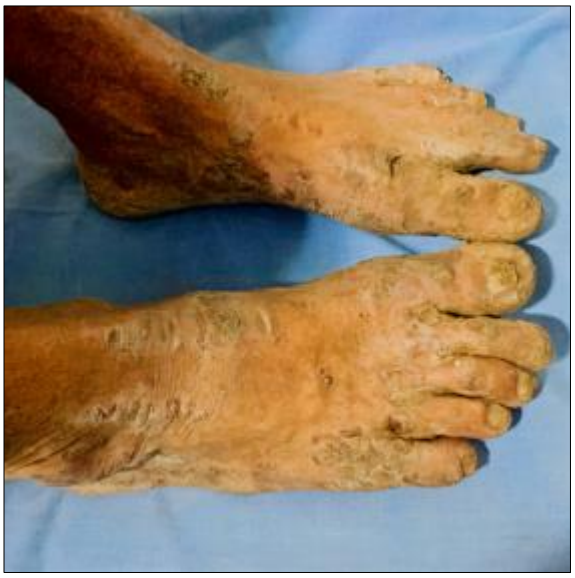

Figure 12 Acral reactions with capecitabine

13.3 Toxicities

Despite the high selectivity of these novel targeted therapies, a range of previously unknown and sometimes unpredictable side effects can emerge. The EGFR is involved in proliferation, survival, and differentiation, and in the skin. The EGFR and its ligands are important in the cycle of keratinocyte maturation[23]. So, as a result of EGFR inhibition, a typically papulopustular (Fig 9, 10) eruption is observed in most patients treated with this family of anti-EGFR agents. Diarrhoea is also a dose-limiting toxicity (DLT) for most small molecule EGFR TKIs. Major mucosal toxicity has been associated with gefitinib.The major side effect of trastuzumab treatment is a reduction in left ventricular ejection fraction (LVEF), in a small proportion of patients even leading to advanced congestive heart failure (CHF), which appears to be at least partly reversible. With Lapatinib the most frequently reported drug-related adverse events were: diarrhea, vomiting, rash, nausea, fatigue and anorexia.

Sorafenib can cause cutaneous toxicity in the form of hand–foot skin reaction (Fig 11, 12), or acral erythema, characterized by painful symmetrical erythematous and edematous areas on the palms and soles, commonly accompanied by paraesthesias.The most common adverse events associated with sunitinib are fatigue, diarrhea, neutropenia, elevation of lipase and anemia.

14. Resistance to Targeted therapy

Most patients with cancers harbouring activating EGFR mutations show marked and sometimes durable responses to EGFR-targeted therapy; despite these initial responses, acquired resistance is a pervasive problem and the median time to progression for patients on EGFR-targeted therapies is approximately 12 months. Both genetic and nongenetic resistance mechanisms have been described[24]. A prominent genetic mechanism is the acquisition of a secondary missense mutation, EGFR T790M. This finding spurred the development of irreversible EGFR inhibitors, with the rationale that such binding would result in greater occupancy of the ATP binding site, thereby inhibiting T790M-mutated EGFR despite its enhanced ATP binding. Similar to EGFR inhibitors, a prominent resistance mechanism involves mutations in the kinase domain of ALK, which cluster into five distinct regions around the active site and impair inhibitor binding.

The most frequent resistant mechanisms associated with Imatinib are the gatekeeper mutations (e.g., T315I) found within the ABL kinase domain, which prevent drug binding,and amplification of the BCR–ABL fusion gene[25]. In addition to mutational activation of ABL, increased expression of drug transporters, such as P-glycoprotein and MDR1 proteins have been reported to promote resistance to Imatinib.

15. Nongenetic mechanisms of drug resistance

(A) A solid tumor often consists of a heterogeneous population of both epithelial and mesenchymal cancer cells. Although slow growing, mesenchymal cancer cells are intrinsically resistant to anticancer agents and may be selected following the drug-promoted eradication of the epithelial cancer cell population.

(B) Similarly, tumors seem to harbor a small number stem cells can divide asymmetrically to generate both a cancer stem cell and a of cancer stem cells that are resistant to anticancer therapies. Following cessation of treatment, the surviving cancer daughter epithelial cancer cell to repopulate the relapsed tumor.

(C) The tumor microenvironment contains a plethora of RTK (Receptor tyrosine kinase) ligands that can provide survival signals by both autocrine tumor cell production and paracrine signaling from the tumor stroma. In the presence of anticancer therapies, the microenvironment may provide a 'prosurvival niche' that promotes the eventual outgrowth of a ligand-responsive subset of tumor cells.

One method by which early detection of treatment resistance can be done is by enumeration and molecular characterisation of circulating tumor cells (CTCs). CTCs are described as cells shed by a primary tumor into vasculature and they keep circulating in the blood stream of cancer patients[26]. The enumeration of CTCs can be used to guide prognosis, assist in measuring response to anticancer therapy, select patients for adjuvant chemotherapy, and detect recurrent disease.Molecular characterisation of CTCs can be used as a surrogate for biological activity of underlying tumour ‘real-time biopsy, elucidate prognostic and predictive molecular features, discover and identify new targets for therapeutic manipulation[27].

16. Conclusion

Molecular targets are widely regarded as the novel treatment agents in the precision oncology era. The cellular signalling targets are important and essential for the tumor proliferation and survival. These novel drugs have limitations in the treatment due to drug resistance. The second generation and third generation drugs are available to overcome the resistance.

Compliance with ethical standards

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Disclosure of conflict of interest

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