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A REVIEW STUDY ON: TARGETED DRUGS IN TUMOR THERAPY

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Abstract

Background: Cancer continues to be a global health challenge, accounting for a significant portion of global mortality.Although focused treatment plans preserve promise for personalised most cancers treatments. Methodology: RI techniques are appealing in clinical practice for early treatment response assessment and patient prognosis. Photoacoustic imaging (PAI) is a new noninvasive molecular imaging modality that uses the photoacoustic effect to generate an ultrasound signal. Results: One biomarker that doctors look for in non-small cell lung cancer is a mutation in the EGFR gene. Combinations of cetuximab and TKI are safe. Following EGFR-TKI resistance in NSCLC, combining an anti-EGFR mAb with an EGFR-TKI resulted in expected safety findings. Conclusions: The use of molecular imaging to predict the efficacy of cancer-targeted therapy early on.targeted therapies have emerged as a promising treatment option for a variety of cancers, including lung cancer, colorectal cancer, and prostate cancer. The discovery of specific molecular targets in cancer cells has resulted in the development of a wide range of targeted drugs that selectively inhibit key pathways involved in tumour growth and progression.

Key words : Targeted cancer therapy, EGFR, TKIs, 2 targeted drugs in tumor therapy

INTRODUCTION

Cancer continues to be a global health challenge, accounting for a significant portion of global mortality. Although traditional cancer treatments such as surgery, chemotherapy, organ transplantation, and radiation therapy have been the mainstays of cancer management, their limitations in efficacy and tolerability have fueled a search for more precise and effective therapeutic approaches [1]. Because of advances in our understanding of the molecular basis of cancer, targeted therapy has emerged as a promising paradigm in cancer treatment. Targeted therapy has ushered in a new era of personalised medicine, in which treatment strategies are tailored to the unique genetic and molecular characteristics of individual tumours. This strategy seeks to exploit specific molecular vulnerabilities within cancer cells while avoiding normal tissues, thereby minimising side effects.

Although targeted therapies hold promise for personalised cancer treatments, therapeutic resistance remains an issue due to tumour cell plasticity, which results in resistance mechanisms such as target mutations, pathway reactivation, and microenvironment interactions. Tumour heterogeneity complicates treatment responses even more. Identifying resistance mechanisms has resulted in better clinical outcomes [2].

Surgery and radiotherapy (RT) are two primary treatment pillars for locoregional and nonmetastatic cancers, respectively, whereas chemotherapeutics can be used at any stage of cancer. Because of their inability to distinguish between tumorous and normal tissues, current chemotherapeutics are frequently limited by undesirable side effects. To reduce these side effects, targeted therapy using monoclonal antibodies or small-molecule inhibitors directed against specific signal transduction pathways for angiogenesis, proliferation, survival, and invasiveness, which are frequently dysregulated in tumour cells, can be developed. The development of targeted therapies is thus a significant step forward in cancer treatment.[3]

2. Literature review

The advancement of next-generation DNA sequencing technologies has allowed for the sequencing of many thousands of cancer genomes, resulting in a thorough characterization of the mutations present in each cancer type. Recurrent mutations are thought to be 'drivers' of the oncogenic phenotype — genes that fuel cancer's continued proliferation. Cancer cells may become 'addicted' to these drivers, and their inhibition frequently results in cell death.[4]

EGFR

The ErbB family of receptor tyrosine kinases includes EGFR. The tyrosine kinase domain is phosphorylated when a ligand binds to its extracellular domain, triggering signalling pathways involved in cell proliferation, angiogenesis, migration, survival, and adhesion. [5] Because of the importance of these pathways in cancer cell growth, EGFR represents a significant therapeutic target for the treatment of metastatic colorectal cancer. Cetuximab become authorised through the

FDA for K-Ras wild-type, EGFR-positive, metastatic colorectal cancer (i) in aggregate with FOLFIRIAs a first-line treatment, (ii) in mixture with irinotecan in sufferers who're refractory to irinotecan-primarily based totally chemotherapy, and (iii)As a unmarried agent in sufferers who've failed oxaliplatin- and irinotecan-primarily based totally chemotherapy or who're illiberal to irinotecan. Cetuximab's anti-metastatic efficacy.[6]

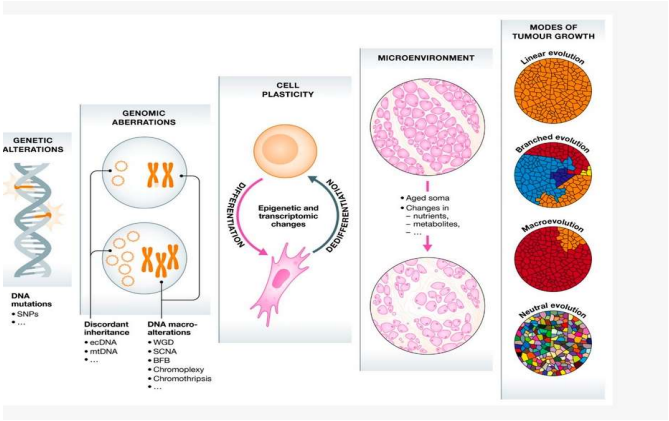

Figure (1): depicts the progression of cancer. Examples of tumour evolution factors ranging from microscopic to macroscopic (left to right).

Initial studies with the EGFR inhibitor gefitinib in advanced EGFR-mutant lung cancer showed a doubling of progression-free survival over chemotherapy, but all patients died from their disease. Almost all other targeted cancer drugs used as single agents in advanced cancers produce comparable results. These clinical findings have sparked a flurry of research into the mechanisms of resistance to these drugs.[7]

Cetuximab, in combination with FOLFIRI, was found to be effective as a first-line treatment for EGFR-positive metastatic colorectal cancers in the CRYSTAL trial. A combination therapy of cetuximab and oxaliplatin-based chemotherapy was also tried as a first-line treatment, but no benefits were found.[8]

Panitumumab, another EGFR antagonist, has also been approved by the FDA as a first-line treatment for wild-type RAS metastatic colorectal cancer in combination with FOLFOX. and as a monotherapy after chemotherapy-induced disease progression. It is not recommended for patients with RAS-mutant metastatic colorectal cancer or those with an unknown RAS mutation status.[9]

T790M mutation in EGFR in response to gefitinib therapy, L1196M mutation in ALK44 in response to crizotinib therapy, T529N mutation in BRAF45 in response to vemurafenib, G2032R mutation in ROS1 after crizotinib46, and Y96D mutation in KRASG12C after adagrasib treatment are examples of on-target gatekeeper mutations. Because of the prevalence of on-target mutations as a mechanism of resistance, next-generation drugs that can inhibit both the original oncoprotein and its resistance-associated mutated form have been developed. [10]

In addition, inhibition of EGFR in lung cancer can result in the activation of other RTKs that can replace EGFR in the activation of the MAPK pathway, conferring acquired resistance.

Amplification of the MET gene is found in 5-22% of EGFR-mutant NSCLC tumours that have acquired resistance to a first-generation or second-generation EGFR tyrosine kinase inhibitor (TKI). MET amplification causes HER3 transactivation, bypassing the EGFR inhibition conferred by gefitinib. Parallel RTK activation via HER2 amplification, in addition to MET gene amplification, can result in acquired resistance to EGFR TKIs.[11]

ALK is a tyrosine kinase receptor encoded on chromosome 2 by an insulin receptor family member. Inversions or translocations cause ALK rearrangements. Exon 20 of ALK was fused with variable regions from partner genes on chromosome. The most common fusion partner in the NSCLC ALK rearrangement is Echinoderm microtubule-associated protein-like 4 (EML4). EML 4-ALK is important in lung tumorigenesis and can be effectively inhibited by ALK selective inhibitors.[12]

ALK rearrangements are responsible for about 7% of molecular aberrations in lung adenocarcinomas. These fusions are more common in never/light smokers. males and those of non-Asian ethnicity.

Crizotinib, an ALK-TKI of the first generation, targets not only ALK but also ROSI and MET. Cricotinib demonstrated a median PFS of 9.7 months and 8.1 months in patients with advanced ALK-positive NSCLC in phase 1 and phase II trials, respectively. Cricotinib was compared to pemetrexed or docetaxel chemotherapy in patients with advanced ALK-positive NSCLC in the phase III PROFILE 1007 trial. Previous study showed that crizotinib outperformed chemotherapy in terms of median PFS (7.7 months vs. 3.0 months) and objective response rate (ORR) (65% vs. 20%). Furthermore, crizotinib demonstrated an acceptable safety profile. Another phase III study, PROFILE 1014, was conducted to compare the efficacy of crizotinib as a first-line treatment for advanced cancer to standard chemotherapy (pemetrexed plus either cisplatin or carboplatin).[13]

Despite crizotinib's superior efficacy, approximately 20% of patients treated with it develop ALK-acquired resistance mutations, with L1196M being the most well-known mechanism. Various ALK-independent resistance mechanisms (e.g., EGFR mutation, mast/stem cell growth factor receptor (KIT) mutation, insulin-like growth factor 1 receptor mutation) have also been identified. Most crizotinib-treated patients relapse within 1-2 years, and approximately 20-30% of ALK-positive NSCLC patients have brain metastases at diagnosis, with the incidence increasing to 50% during cancer progression. Crizotinib has poor CNS penetration, resulting in chronic CNS metastasis.[14]

Second-generation ALK-TKIs, such as alectinib, ceritinib, and brigatinib, have demonstrated efficacy.

Improved CNS penetration. An ALEX study compared alectinib to crizotinib as a treatment.[15]

Alectinib was approved as first-line therapy for patients with advanced ALK-positive NSCLC who demonstrated superior CNS activity and delayed CNS progression. When compared to crizotinib, alectinib was also shown to be a potential first-line treatment option. An ASCEND-4 study was conducted to compare the efficacy of ceritinib as first-line therapy to chemotherapy in advanced AL.K-rearranged NSCLC. The median PPS with ceritinib was 16.6 months and 8.1 months with chemotherapy. The efficacy of ceritinib was compared to chemotherapy in ALK-

rearranged NSCLC patients who had previously progressed following chemotherapy and crizotinib treatment in the ASCEND-5 trial. [16] Ceritinib had a significantly longer median PPS (5.4 months vs. 4.6 months for chemotherapy), demonstrating that it is a more potent ALK inhibitor when compared to chemotherapy after crizotinib failure. When compared to crizotinib, another second-generation ALK-TKI, brigatinib, also proved to be a promising TKI for patients with ALK-positive NSCLC. Brigatinib had a significantly higher 12-month PFS than in comparison to crizotinib (67% vs. 43%)

Lorlatinib has been proposed as a subsequent and potentially first-line therapy for ALK-positive NSCLC patients due to its ability to penetrate the CNS and cover AL.K mutations. When lorlatinib was compared to crizotinib as first-line therapy for advanced ALK-positive NSCLC patients, the lorlatinib group had a longer PFS and a higher intracranial response.[17]

1. Methodology

Both the World Health Organisation (WHO) response criteria and the Response Evaluation Criteria in Solid Tumours use changes in tumour size as determined by imaging techniques such as CT, MRI, and positron emission tomography (PET) to evaluate the efficacy of anticancer treatment. [18]

The MRI parameters, particularly their post-treatment changes, are sensitive to the biological changes caused by cancer-targeted therapies. These MRI techniques are appealing in clinical practice for early treatment response assessment and patient prognosis prediction due to their radiation-free nature. [19]

3. 1 Imaging with optical:

The evidence for using optical imaging to predict the efficacy of cancer-targeted treatment comes from preclinical research rather than human studies. In the preclinical setting, BLI has been widely used for cancer detection, disease progression monitoring, and assessing the efficacy of anticancer treatment in vivo. [20]

3. 2 Imaging using photoacoustics:

Photoacoustic imaging (PAI) is a new noninvasive molecular imaging modality that uses the photoacoustic effect to generate an ultrasound signal.When laser pulses are introduced to a material, a number of the electricity is absorbed and convertedto heat, causing a thermoelastic expansion that produces an ultrasonic signal from which images can be generated.

PAI, a hybrid of optical imaging and ultrasound imaging, combines the optical property's high contrast and sensitivity with high ultrasonic spatial resolution in a single imaging modality. Furthermore, the unprecedented imaging depth (up to centimetres) makes this technique promising for a variety of clinical applications. PAI can be used to analyse oxygenated and deoxygenated haemoglobin, lipids, melanin, and water, among other endogenous contrast agents.[21]

3.3 Ultrasound imaging:

Ultrasound is a technique that creates anatomical images by using high-frequency sound waves. It has several advantages, including high availability, low radioactivity, and low cost. These advantages make it suitable for repeated use in clinical practice. Ultrasound can be used to assess blood flow in tumours using the Doppler technique. More importantly, using contrast agents such as microbubbles, dynamic contrast-enhanced ultrasound (DCE-US) can measure longitudinal changes in hemodynamic parameters (e.g. , perfusion, flow velocity) and morphological parameters (e.g., blood volume, vascular heterogeneity) of a given tumour compared to pretreatment baseline findings. The importance of tracking changes in these parameters for monitoring the therapeutic response induced by anti-angiogenic therapies has been investigated.[22]

2. Results

One biomarker that doctors look for in non-small cell lung cancer is a mutation in the EGFR gene. Combinations of cetuximab and TKI are safe. Following EGFR-TKI resistance in NSCLC, combining an anti-EGFR mAb with an EGFR-TKI resulted in expected safety findings. Sequential EGFR family receptor blockade with afatinib, followed by cetuximab plus afatinib, demonstrated activity in closely pretreated sufferers with received resistance to erlotinib or gefitinib, with a predictable protection profile. In patients with acquired resistance to TKIs caused by EGFR mutation, dual inhibition of EGFR with EGFR-TKIs and anti-EGFR mAbs has shown promising anti-tumor activity. Cetuximab/EGFR-TKI combination therapy has demonstrated clinical benefit and a manageable safety profile, implying that cetuximab in combination with second- and third-generation TKIs could play a role as a second- and/or subsequent-line treatment option for patients with NSCLC who have specific EGFR mutations conferring resistance to prior TKI therapy. The frequent somatic mutation and/or overexpression of EGFR in malignant cells versus normal cells opens up a therapeutic window for targeting the receptor. Targeting strategies differ and frequently take advantage of mutant receptors' cancer-associated expression. Although EGFR is important in the biology of many different tumours, its specific genetic alterations vary according to tumour type. More specifically, certain mutations are common in some tumours but uncommon in others. Somatic mutations in the kinase domain, for example, are common in non-small cell lung cancer (NSCLC) but uncommon in other types of cancer, such as glioblastoma multiforme (GBM).

3. Discussion

The use of molecular imaging to predict the efficacy of cancer-targeted therapy early on. Traditional predictive biomarkers for targeted therapy are based primarily on invasive tissue biopsy and subsequent pathological analysis. Because only a limited amount of tissue can be biopsied and tumour heterogeneity exists, conventional histopathological biomarkers obtained from a single lesion are not always predictive of response to targeted therapy, particularly in patients with multiple metastatic tumours. The current gold standard for assessing the efficacy of targeted treatment after therapy is the use of the RECIST criteria, a method based on tumour size change.[23]

In the following ways, the novel molecular imaging technique outperforms conventional imaging techniques for cancer-targeted therapy: It enables whole-body imaging, such as immuno-PET, to better demonstrate intra- and inter-tumoral heterogeneity of targeted molecule expression. This allows for the prediction of lesion-specific treatment efficacy. It allows for the imaging of early changes in a tumor's functional status (usually several days after treatment), which may reflect the response to targeted therapy and allow for the early detection of treatment resistance and prediction of long-term efficacy.[24]

In this field, the most commonly studied targets are VEGF, HER2, EGFR, ER, and PD-1/PD-L1. Early clinical trials used immuno-PET binding to these targets to assess anti-cancer targeted treatment efficacy and predict patient prognosis. Early results showed that these tools have a high potential for translation into clinical practice. However, due to regulatory constraints, clinical translation of new radiotracers is difficult in many countries, including China. Multimodality molecular imaging may be a promising approach for improving predictive accuracy in assessing the efficacy of targeted treatment.[25]

4. Conclusions

Finally, targeted therapies have emerged as a promising treatment option for a variety of cancers, including lung cancer, colorectal cancer, and prostate cancer. The discovery of specific molecular targets in cancer cells has resulted in the development of a wide range of targeted drugs that selectively inhibit key pathways involved in tumour growth and progression. Overall, targeted therapies have transformed cancer treatment, allowing for more personalised and effective approaches. However, challenges such as resistance mechanisms, biomarker identification, and optimal combination strategies remain to be addressed in order to improve the efficacy and clinical impact of targeted therapies. Furthermore, it should be noted that some people are extremely sensitive to targeted therapies, resulting in specific and severe side effects. [26]

Continued research and collaboration among academic institutions, industries, and regulatory authorities will be critical in advancing the field of targeted therapies and, ultimately, improving the outcomes of cancer patients.

REFERENCES:

1. Ramos, P.; Bentires-Alj, M. Mechanism-Based Cancer Therapy: Resistance to Therapy, Therapy for Resistance. Omvyene 2015, 34,617-3626,
2. Xu, M. J., Johnson, D. E. & Grandis, J. R. EGFR-targeted therapies in the post-genomic era. Cancer Metastasis Rev. 36, 463–473 (2017).
3. Hudson, J. M. et al. Dynamic contrast enhanced ultrasound for therapy monitoring. Eur. J. Radiol. 84, 1650–1657 (2015).
4. Steinberg, I. et al. Photoacoustic clinical imaging. Photoacoustics 14, 77–98 (2019).
5. Teng, F. F., Meng, X., Sun, X. D. & Yu, J. M. New strategy for monitoring targeted therapy: molecular imaging. Int. J. Nanomed. 8, 3703–3713 (2013).

6. Wirsching, H. G. et al. MRI and (18)FET-PET predict survival benefit from bevacizumab plus radiotherapy in patients with isocitrate dehydrogenase wild-type glioblastoma: results from the randomized ARTE Trial. Clin. Cancer Res. 27, 179–188 (2021).
7. Vendramin, R.; Litchfield, K.; Swanton, C. Cancer evolution: Darwin and beyond. EMBO J. 2021, 40, 108389.
8. Boxerman, J. L. et al. Prognostic value of contrast enhancement and FLAIR for survival in newly diagnosed glioblastoma treated with and without bevacizumab: results from ACRIN 6686. Neuro Oncol. 20, 1400–1410 (2018).
9. Haslam, A., Kim, M. S. & Prasad, V. Updated estimates of eligibility for and response to genome-targeted oncology drugs among US cancer patients, 2006–2020. Ann. Oncol. 32, 926–932 (2021)
10. El-Abtah, M. E. et al. Myo-inositol levels measured with MR spectroscopy can help predict failure of antiangiogenic treatment in recurrent glioblastoma. Radiology 302, 410–418 (2022).
11. Cunningham, D.; Humblet, Y., Siena, S.; Khayat, D., Bleiberg, H., Santero, A.; Bets, D., Mueser, M., Harstrick, A.; Verslype, C., et al. Cetuximab Monotherapy and Cetuximab plus Irinotecan in Irinotecan-Refractory Metastatic Colorectal Cancer. N. Engl. I. Med 2004, 351, 337-345
12. Bodoky, G.; et al. Cetuximab and Chemotherapy as Initial Treatment for Metastatic Codorectal Cancer. N. Engl. J. Mol. 2009, 350, 1408-1417.
13. Kenny, S.L., et al. Addition of Cetuximab to Oxaliplatin-Based First-Line Combination Chemotherapy for Treatment of Advanced Colorectal Cancer: Results of the Randomised Phase 3 MRC COIN Trial. Lancet 2011, 377, 2103-2114.
14. Soria J-C, Ohe Y, Vansteenkiste Reungwetwattana T, Chewaskulyong B, Lee KH, et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. N Engl J Med 2018;378(2):113-25.
15. Wu Y-L, Cheng Y, Zhou X, Lee KH, Nakagawa K, Niho S, et al. Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050): a randomised, open-label, phase 3 trial. Lancet Oncol 2017;18(11):1454-66.
16. Pao W, Chmielecki J. Rational, biologically based treatment of EGFR mutant non small-cell lung cancer. Nat Rev Cancer 2010;10(11):760-74.
17. Jiang Y, Zhang J, Jiang X, Cheng L, Liao X, Li Y, et al. Sequential use of EGFR- tyrosine kinase inhibitors based upon EGFR mutation evolution achieves long-term control in a non-small cell lung cancer patient: a case report. Ann Palliat Med 2021; 10(6):7051-6.
18. Yu HA, SK, Drilon Borsu L., Riely GJ, Arcila ME, et al. Acquired resistance of EGFR-mutant lung cancer to a T790M-specific EGFR inhibitor: emergence of a hird Mutation (C797S) in the EGFR tyrosine kinase domain. JAMA Oncol 2015:(7):982.

19. Janne PA, Baik C, Su WC, Johnson ML., Hayashi H, Nishio M, et al. Efficacy and safety of patritumab deruxtecan (HER3-DXd) in EGFR inhibitor-resistant, EGFR- mutated non-small cell lung Cancer Discov. 2022:12:74-89.
20. Yu HA, Arcila ME, Rekhtman N, Sima CS, Zakowski MF, Pao W, et al. Analysis of tumor specimens at the time of acquired resistance to EGFR-TKI therapy in 155 patients with EGFR-mutant lung cancers. Clin Cancer Res. 2013;19:2240-47.
21. Marchetti, A: Felicioni, L.; Malatesta, S.; Sciarrotta, M.G., Guetti, L, Chella, A.; Viola, P; Fullara, C., Mucilli, F; Buttitta, F Clinical Features and Outcome of Patients with Non Small Cell Lung Cancer Harboring BRAF Mutations. J. Clin. Oncol. 2011, 29, 3574-3579.
22. Xi, Y. Xu, P. Global Colorectal Cancer Burden in 2020 and Projections to 2040. Traus! Oncol. 2021, 14, 101174, CrosRef 62 Keenan, JL, Frizelle, F.A. Biomarkers to Detect Early-Stage Colorectal Cancer. Biomedicines 2022, 10, 255
23. Santarpia M, Liguori A, Karachaliou N, Gonzalez-Cao M, Daffina MG, D'Aveni A, et al. Osimertinib in the treatment of non-small-cell lung cancer. design, development and place in therapy. Lung Cancer (Auckl) 2017:8:109-25.
24. Niederst MJ, Hu H, Mulvey HE, Lockerman EL., Garcia AR, Piotrowska Z, et al. The allelic context of the C7975 mutation acquired upon treatment with third- generation EGFR inhibitors impacts sensitivity to subsequent treatment strategies. Clin Cancer Res. 2015;21:3924-33.
25. Watanabe K, Saito R, Miyauchi E, Nagashima H, Nakamura A, Sugawara S, et al. Monitoring of plasma EGFR mutations during osimertinib treatment for NSCLC patients with acquired T790M mutation. Cancers (Basel). 2023;15
26. Rosell R, Carcereny E, Gervais R, Vergnenegre A, Massuti B, Felip E, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol 2012;13(3): 239-46.