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Review

Next-generation epidermal growth factor receptor tyrosine kinase inhibitors in epidermal growth factor receptor -mutant non-small cell lung cancer

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ABSTRACT

Since the discovery of sensitizing *EGFR* mutations as a predictive marker of sensitivity to EGFR tyrosine kinase inhibitors (TKIs), the field of targeted therapy in non-small cell lung cancer (NSCLC) has been revolutionized. Patients harbouring these sensitizing mutations treated with EGFR TKI have derived significant clinical outcome when compared with standard platinum based chemotherapy doublets. However disease progression invariably occurs at a median of about 9–13 months from initiation treatment, if acquired resistance commonly due to the development of EGFR T790M mutation. A novel class of "third generation" EGFR TKIs have been developed that is sensitising and T790M mutant-specific whilst sparing WT EGFR, representing a significant breakthrough in the treatment in NSCLC patients with acquired resistance harboring these genotypes. Early phase clinical data suggest the third generation EGFR TKIs such as osimertinib, rociletinib, and HM61713 are highly efficacious and well tolerated. Another promising class of EGFR TKI such as AZD3759 has been designed to penetrate blood brain barrier to treat brain metastases and leptomeningeal disease and has showed promising responses in patients with brain metastases. Acquired resistance to third generation EGFR TKIs has been reported including EGFR C797S. Given its non-invasive nature, plasma ctDNA is being explored as a possible approach to detect T790M mutation and to also inform on novel molecular mechansims of tertiary resistance to third generation EGFR TKIs. An understanding of the mechanisms of acquired resistance to the third-generation EGFR TKIs will greatly aid in the development of the next generation of EGFR TKIs.

1. Introduction

Lung cancer is a leading cause of cancer death worldwide, causing 1.4 million deaths annually [1]. In patients with advanced stage non-small cell lung cancer (NSCLC), prognosis is poor with a median survival of 8 months when treated with platinum based chemotherapy [2]. The discovery of somatic activating epidermal growth factor receptor (EGFR) gene mutations as a target for tyrosine kinase inhibitors (TKIs) had changed the paradigm of care for advanced NSCLC patients [3]. In unselected population, somatic *EGFR* mutations are common in East Asian patients, with a frequency of 30–50% [4,5] whereas the frequency is only about 10% in Caucasian patients [5]. Activating *EGFR* mutations drive signaling pathways, resulting in cell growth and survival. The two commonest *EGFR* mutations are exon 19 (in-frame) deletion and exon 21 point mutation (L858R), comprising about 90% of known activating somatic *EGFR* mutations [6] and they predict for sensitivity to EGFR tyrosine kinase inhibitors (TKIs). In studies of untreated advanced stage NSCLC with sensitizing *EGFR* mutations treated with erlotinib, gefitinib or afatinib, outcomes were superior to chemotherapy in terms of efficacy and quality of life, leading to the regulatory approval of EGFR TKIs and the acceptance for use in the first line setting of *EGFR* mutant NSCLC [3,7–9].

Patients treated with EGFR TKIs will invariably develop acquired resistance. Mechanisms of acquired resistance to EGFR TKIs include secondary mutation in *EGFR* (50-60%), bypass or alternative pathway activation (1–25%) and histological/phenotypic transformation (5–10%), and unknown in 20–30% [10,11]. The commonest

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cause of acquired mechanism of resistance is the secondary mutation in EGFR where methionine was substituted for threonine at position 790 (T790M) at exon 20 [10,11]. The bulky methionine side chain substitution results in the steric hindrance of binding of first generation EGFR TKIs to the ATP-pocket [12] and also a higher affinity to ATP as substrate compared to EGFR TKIs [13].

2. Second Generation EGFR TKIs

The second generation of EGFR TKIs (afatinib and dacomitinib) are irreversible EGFR inhibitors designed to overcome T790M resistance [14]. Despite the theoretical advantages and promising pre-clinical data, the second generation EGFR TKIs were not active in overcoming T790M resistance. This is mainly due to a narrow therapeutic window resulting in gastrointestinal (diarrhea, mucositis) and dermatologic toxicity due to wild-type (WT) EGFR inhibition [14].

Afatinib however is approved in first line treatment for advanced NSCLC patients harbouring sensitizing *EGFR* mutations with an improvement in PFS and overall survival with afatinib versus cisplatin and pemetrexed [9]. In patients treated with prior chemotherapy, and EGFR TKI, combination afatinib and cetixumab resulted in an ORR of 29% and PFS was 4.7 months. No significant difference in the ORR between the T790M-positive and T790-M-negative patients was seen (32% vs 25%, $P = 0.341$). These results highlighted two important points. Firstly this combination was effective regardless of the T790M status. Secondly the result also confirmed that, despite acquiring resistance to EGFR TKI, the tumours were still dependent on EGFR signalling for growth and survival. Side effects included skin rash (90% all grade) and diarrhea in (71%) [15].

3. Third generation EGFR TKIs

The third generation TKIs such as osimertinib (AZD9291), rociletinib (CO-1686), HM61713, EGF816, and ASP8273 are mutant selective and EGFR wild type (WT) sparing, targeting sensitising *EGFR* mutations as well as T790M EGFR (Table 1). Furthermore they have very low inhibitory effect on WT EGFR, thus overcoming the toxicity limitation seen with the first and second generation EGFR TKIs (Table 1). WZ4002 was one of the earliest compounds investigated [16]. *In vitro*, WZ4002 was 30-100 times more potent against EGFR T790M and 100 times less potent against WT EGFR (Table 1) and similar potency was seen *in vivo* using T790M driven murine lung models. WZ4002 is currently not in clinical development.

3.1. Osimertinib (Tagrisso, AZD9191)

Osimertinib (AstraZeneca) is a mono-anilino-pyrimidine compound that is structurally different from other third generation EGFR TKIs [17] (Table 1). Osimertinib targets the cysteine-797 residue in the ATP binding site of the EGFR kinase irreversibly through covalent bond formation. Significant activity was demonstrated in tumor xenograft and transgenic models [17].

In a phase I/II multicenter study (AURA trial), 253 patients (Asian (61.7%, 156/253) and Western (35.6%, 90/253) with locally advanced or metastatic NSCLC with known sensitizing *EGFR* mutations or had derived clinical benefit as per Jackman's criteria and documented disease progression on EGFR TKIs were treated with osimertinib.This study recruited 31 patients into the escalation cohorts (20–240 mg) followed by a dose expansion cohort would be opened. In the expansion cohort, all patients underwent a tumor biopsy to determine T790M mutation status. The maximal tolerated dose (MTD) was not reached at any dose level and 80 mg daily was the recommended monothersapy dose.

Table 1
Pre-clinical efficacy data measured by IC50 (nM) of selected first-, second-, third-generation EGFR TKIs in selected lung cancer cell lines.

EGFR mutation	$EGFR^{del19}$	$EGFR^{del19}$	$EGFR^{del19}$	$EGFR^{L858R}$	$EGFR^{del19/T790M}$	$EGFR^{L858R/T790M}$	$EGFR^{WT}$	$EGFR^{WT}$	$EGFR^{WT}$	$EGFR^{WT}$	$EGFR^{WT}$	$EGFR^{WT}$
Cell lines	HCC827	H1650	PC9	H3255	HCC827-EPR	NCI-H1975	A431	NCI —H2073	LoVo	NCI-H1299	NCI-H358	NCI-H1666
Gefitinib [17]	NA	16, 19	7 (5, 11)	11, 12	NA	3102 (1603, 6001)	60, 88	61 (34, 110)	59 (42, 82)	NA	NA	NA
Erlotinib [22]	<14	NA	21	NA	NA	>5000	<7	NA	NA	NA	NA	NA
Dacomitinib [17]	NA	0.04, 0.06	0.7 (0.5, 1)	1.2, 1.3	NA	40 (24, 65)	51, 22	26 (7, 99)	12 (8, 17)	NA	NA	NA
Afatinib [17]	NA	0.6, 3	0.6 (0.5, 0.8)	1, 0.8	NA	22 (15, 31)	27, 40	25 (5, 129)	15 (10, 24)	NA	NA	NA
WZ4002 [16]	5	NA	36	89	NA	47	NA	NA	NA	NA	NA	NA
AZD9291 [17]	NA	14,12	17 (13, 22)	60, 49	NA	15 (10, 20)	2376, 1193	1865 (872, 3988)	480 (320, 720)	NA	NA	NA
Rociletinib [22]	187 ± 88	NA	211	NA	180 ± 55	62 ± 34	>4331	NA	NA	>2000	>2000	NA
ASP8273 [30]	NA	46	NA	NA	NA	26	NA	NA	NA	NA	NA	230
HM61713 [25]	9.2	NA	NA	NA	NA	10	NA	NA	NA	NA	2225	NA

NA, not available.