CHAPTER 4B

Transformation to a squamous cell carcinoma phenotype of an EGFR-mutated NSCLC-patient after treatment with an EGFR-tyrosine kinase inhibitor

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Activating mutations in the epidermal growth factor receptor (EGFR) are detected in approximately 10% of Caucasian and up to 50% of Asian patients with non-small cell lung cancer (NSCLC) (1). EGFR-tyrosine kinase inhibitors (TKIs) constitute the preferred first-line treatment for these patients. Unfortunately, all patients eventually develop resistance to EGFR-TKI after a median of 13 months (2). Several different resistance-mechanisms have been demonstrated in biopsies of recurrent tumours after EGFR-TKI treatment. Among these are the T790M secondary resistance mutation on EGFR exon 20 and amplification of alternative pathways such as MET and HER2, but also morphological changes with epithelial-to-mesenchymal transition and transformation to a small cell lung cancer (SCLC) phenotype (2).

Here we report a case with transformation to a squamous cell carcinoma (SqCC) phenotype. To the best of our knowledge, this is the first report on transformation to SqCC after acquired TKI-resistance in EGFR-mutated NSCLC.

In August 2013, a 63-year old Caucasian non-smoking female was diagnosed with NSCLC (T2bN3M1b). A biopsy from the right lower lobe (RLL) revealed an adenocarcinoma (p63 immunohistochemistry (IHC)-negative, TTF-1 IHC-positive) (Figure 1A) and mutation analysis of EGFR (exons 18-21) showed an exon 21 mutation (c.2573T>G; p.L858R). She was treated with erlotinib until she developed progression in January 2014. Second-line chemotherapy (cisplatin/pemetrexed) was initiated, on which she progressed after two cycles. At this time, a rebiopsy from the same lesion in the RLL was performed and histopathological analysis revealed SqCC (p63 IHC-positive, TTF-1 IHC- and pas-d stain-negative) (Figure 1B). This time, a panel of genes was evaluated for mutations using TSACP-MiSeq-NGS (3), demonstrating the identical mutation in EGFR exon 21 (c.2573T>G; p.L858R) and a mutation in PIK3CA exon 20 (c.3140A>G; p.H1047R). No mutations in other genes of the oncopanel, such as KRAS, NRAS, HRAS, BRAF, ALK, ERBB2, FGFR1, AKT, MEK or PTEN, were detected. She then started gefitinib in April 2014, on which she progressed after four months. Subsequently she was treated with chemotherapy (carboplatin/gemcitabine), but during the second cycle symptomatic brain metastases were detected. She refused further treatment and died in October 2014.

Intratumour heterogeneity describes the phenomenon that tumour lesions within one individual may harbour different morphological and genetic characteristics (4). It is highly likely that intratumour heterogeneity plays a major role in the development of acquired resistance to targeted therapies. For transformation to SCLC during EGFR-TKI treatment, it has been hypothesized that a small population of neoplastic cells with a SCLC phenotype is already present at start of EGFR-TKI treatment. During this treatment, the sensitive (NSCLC) tumour cells are efficiently eliminated, providing the small clone of resistant (SCLC) tumour cells the opportunity to proliferate. The initial mutation remains detectable in the SCLC.
tumour cells. This ‘selection-hypothesis’ may also apply to this case of ‘transformation’ to SqCC as the identical EGFR-mutation was detected both in the original biopsy and in the rebiopsy. It is known that EGFR-mutations in SqCC are rare and EGFR-TKI treatment is less effective in EGFR-mutated SqCC compared to EGFR-mutated adenocarcinoma (5).

PIK3CA mutations are associated with the SqCC histological subtype (6). Unfortunately, the amount of remaining tumour tissue of the original biopsy was not sufficient for extensive mutation analysis, including PIK3CA. We therefore cannot exclude that this mutation was initially present. Nonetheless, this case emphasizes that tumour cell characteristics are dynamic and may change during (targeted) treatment (7). In order to tailor treatment to the individual NSCLC-patient, it is therefore necessary to perform molecular monitoring during the course of disease, such as rebiopsy of a growing lesion after targeted treatment, to remain optimally informed about the tumour characteristics.

Figure 1:
First biopsy stained with H&E (A), TTF1 (B, arrow: tumour nuclei +), PAS-D (C, tumour nuclei ±) and p63 (D, arrow: tumour nuclei-) favouring adenocarcinoma (i.e., TTF1 ++; mucin ±; p63 -).
Second (re)biopsy stained with H&E (E, G, small arrows: cytoplasmic bridges), TTF1 (F, tumour nuclei-) and p63 (H, tumour nuclei +) favouring squamous cell carcinoma (i.e., TTF1-; p63++).
REFERENCE LIST


