TARGETED THERAPIES IN NON- SMALL-CELL LUNG CANCER (NSCLC)

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Following the exciting results obtained in the treatment of CD117+ advanced GIST by imatinib and in HER2+ adiuvant breast cancer by herceptin, a number of molecular target drugs have been tested in solid tumours, sometime failing in clinical trials. In advanced NSCLC chemotherapy efficacy appears to have reached a plateau, increasing over the last two decades, only a 2-week in the median of median survival. The characterization of molecular abnormalities has identified potential therapeutic targets also in NSCLC, mainly mutation in EGFR that could be a predictive marker for selecting treatment with EGFR TK inhibitors,as gefitinib and erlotinib. Gefitinib is the first selective inhibitor that targets the mutant proteins, approved after phase II trials (IDEAL 1, IDEAL 2) for " third-line" treatment, but phase III clinical trial (ISEL trial) raise serious questions about whether it prolongs survival time. However, it may work in just subset of cases. Erlotinib is approved for "second-line" treatment . In three phase II trials assessing second-line treatment , gefitinib demonstrated an ORR of 10.3%-18.3% while erlotinib 12.3% and a median survival of 7.8 mo and 8.4 mo respectively. In the phase III BR.21 trial, in pretreated patients, the response rate was 8.9% in erlotinib group vs < 1% in placebo group (p 0.001) , the median PFS 2.2 mo vs 1.8 mo (p 0.001) and the OS 6.7 mo vs 4.7 mo (HR 0.70; p 0.001). Activating mutation in the EGRF gene have been found to predicti a response. In USA , actually, erlotinib has replaced in gefitinib , except in patients where gefitinib has had a proved response. Recently, has been proposed a test (cost about 975$) to detect EGFR espression, designed to help predict which NSCLC may respond best to some therapies, obviously including gefitinib and erlotinib. Negative results were obtained in phase III trials (INTACT 1, INTACT 2, TRIBUTE and TALENT), when both gefitinib and erlotinib were combined with chemotherapy. A reason for these disappointing results is the inherent ability of cancer cells to escape one single block by facilitating others GF-pathways for growth and survive. Moreover, since selective mono-target drugs seem to have limited activity, simultaneous multi-target inhibitors could be more effective. In phase I-II studies, Erlotinib, Bevacizumab, Erbitux, Bortezomib, ZD 6474 and ZD 2171 antiangiogenic TK inhibitors, are now tested in douplets combination, showing some activity as the 1-yr survival of 52% with the simultaneous erlotinib-bevacizumab. Multitarget inhibiting VEGFR, PDGFR, Kit, FLT3, RET as Sunitinib and Sorafenib (alone or in combination with bevacizumab) have provocative activity, at least similar to currently approved agents. In conclusion, all the above-cited knowledges have paved the road of the molecular/genetic tailored therapies in NSCLC, but suggest that, when necessary, the testers must return to their basic laboratory in order to deepen some still unclear key points. As example, a few centers have started testing for the most common mutations in EGFR; any way what to do if negative? Some patients, indeed, with responses to gefitinib/erlotinib have not detectable EGFR mutation. Actually , gefitinib does not prolong survival; erlotinib prolong survival (about 2 months); mutation in exon 19 and 21 are response-predictive; mutation in K-ras is predictive the treatment inefficacy. Problems : proper selection of the patients?, target therapy "not-target"? , chemotherapy + EGFR target-agents target the same cell?, molecular heterogeneity?.