A time to test, a time to treat

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J Thorac Dis 2012;4(2):223-225. DOI: 10.3978/j.issn.2072-1439.2012.03.13

Nearly thirty years ago, the Epidermal Growth Factor Receptor (EGFR) was identified as a suitable target for cancer therapeutics (1,2). Over the subsequent three decades, oncologists have sought to harness the observation that the proliferation of some malignant cells is dependent on activation of the EGFR and subsequent downstream propagation of signaling via the intracellular tyrosine kinase. Drugs such as tyrosine kinase inhibitors (TKIs) targeting this pathway were tested in a variety of malignancies, with occasional excellent responses seen in patients with non-small cell lung cancer (NSCLC) (3). A variety of different clinical (Asian, non smokers, women) (4-7) and molecular explanations (EGFR protein expression, EGFR copy number) (8-10) were given for this selective benefit, prior to the realization that mutations in the kinase domain of the EGFR (EGFR-MT) were probably largely responsible for these dramatic responses (11-14).

Around the same time as the identification of EGFR-MT, results from the BR21 trial of erlotinib in the treatment of metastatic NSCLC that had previously progressed despite chemotherapy were published, showing a marginal progression free survival (PFS) and overall survival (OS) benefit in otherwise unselected NSCLC patients (15). Although the clinical significance of the PFS improvement of a few weeks was debatable, and a similar trial of gefitinib in this population was negative (15), OS was improved and erlotinib was approved by the FDA. Consequently, given lack of access to EGFR-MT testing, combined with concerns regarding cost and treatment delays (16,17), many clinicians have chosen to use erlotinib in the unselected treatment of untested, previously treated NSCLC patients, reserving EGFR-MT testing for those who fit phenotypic stereotypes (18). The European EURTAC trial (19), published in the Lancet Oncology in January, alongside a body of evidence from East Asia gives cause for reconsideration of this strategy (20-23).

In EURTAC, patients with metastatic untreated NSCLC with EGFR-MTs were randomized to erlotinib (150 mg) or a cisplatin-based doublet (docetaxel or gemcitabine). Patients ineligible to receive cisplatin were treated with carboplatin, and patients receiving chemotherapy were treated with at most four cycles. Hospitals in France, Italy and Spain screened 1,227 patients for the trial, detecting 224 EGFR-MT patients (17.6%), of whom 174 patients were eligible for randomization on a 1:1 basis to either treatment arm. Impressively, the investigators were able to get results from EGFR mutation testing within 7 days from more than 40 centers involved in the trial.

At a preplanned interim analysis, the study was halted due to benefit in the erlotinib arm. The primary end point of progression free survival (PFS) was met, with an improvement in PFS of 9.7 months in patients treated with erlotinib compared to 5.2 months in the chemotherapy arm (HR=0.37, P<0.0001). Overall survival was similar between the two groups, 19.3 months in the erlotinib group, 19.5 months in the standard chemotherapy group. However cross-over was permitted between the groups, and less than half the study population had died at the time of the final analysis. The response rate of 64% in the erlotinib arm was superior to that in the standard chemotherapy arm (18%). These results are similar to those seen in the previously published studies of EGFR-TKI use in first line treatment of EGFR-MT NSCLC in Asian populations (OPTIMAL, NEJ002, WJOTG3405 and IPASS), confirming the advantages of treating patients with EGFR-MT NSCLC with an EGFR-TKI first line, regardless of ethnicity, or choice of EGFR-TKI (Table 1). Beyond chance effects, differences in response rates and PFS to both the TKI and chemotherapy in these trials may be possibly explained by differing sensitivity to the type of chemotherapy used in each of the comparator arms, and differing frequencies of specific EGFR-MTs {Rosell, 2010 #1153;Sun, 2011 #1154} between trials.

Notably all of these studies have failed to show a survival advantage between first line EGFR-TKI and platinum based chemotherapy, but these should not reinforce complacency regarding EGFR-MT testing. These trials provide several

No potential conflict of interest.

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Submitted Mar 09, 2012. Accepted for publication Mar 16, 2012.
Available at www.jthoracdis.com

ISSN: 2072-1439

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Table 1. Effects of an EGFR-TKI first line in patients with EGFR-MT NSCLC.

Trial	EGFR-TKI	Response Rate		PFS		OS	
		EGFR-TKI	Chemo	EGFR-TKI	Chemo	EGFR-TKI	Chemo
EURTAC (19)	Erlotinib	58%	15%	9.7	5.2	19	19
OPTIMAL (23)	Erlotinib	83%	36%	13.1	4.6	-	-
NEJ002 (21)	Gefitinib	74%	31%	10.8	5.4	30.5	23.6
WJTOG (22)	Gefitinib	62%	31%	9.2	6.3	-	-
IPASS (20)*	Gefitinib	71%	47%	9.5	6.3	22	22

*IPASS included both EGFR-MT and EGFR wild type patients, but only EGFR-MT results are shown here. Chemo: chemotherapy; PFS: Progression free survival (months); OS: Overall survival (months).

Table 2. Adverse events of an EGFR-TKI first line in patients with EGFR-MT NSCLC.

TRIAL	Grade 3/4 adverse events		Treatment discontinuation		Not treated with EGFR-TKI post chemotherapy
	EGFR-TKI	Chemo	EGFR-TKI	Chemo	
EURTAC (19)	45%	67%	13%	23%	24%
OPTIMAL (23)	17%	65%	1%	6%	-
WJTOG (22)	-	-	16%	12.5%	-
NEJ002 (21)	41%	71.7%	-	-	5%
IPASS (20)*	29%	61%	6.9%	13.6%	39%

*IPASS included both EGFR-MT and EGFR wild type patients, but only EGFR-MT results are shown here. Chemo: chemotherapy; PFS: Progression free survival (months); OS: Overall survival (months).

reasons why delaying EGFR-TKI therapy until the second line may be suboptimal treatment of EGFR-MT NSCLC. As detailed in Table 2, apart from the WJTOG 3,405 study, there were higher rates of grade 3-4 adverse events in the chemotherapy arm of each study and higher rates of treatment discontinuation. Both OPTIMAL and IPASS have additionally published quality of life data strongly supporting EGFR-TKI use over chemotherapy. Even more significantly, between 5-39% of patients receiving first line chemotherapy never received second line EGFR-TKI therapy, denying them access to a highly efficacious and tolerable therapy. Conversely, patients who are EGFR wild type do much better receiving first line chemotherapy, rather than an EGFR-TKI (20,24).

Of course there are barriers to obtaining suitable tissue from patients with metastatic NSCLC, and barriers to processing EGFR-MT testing within an acceptable time frame. Although in the EURTAC study testing was performed within 7 days, this may not be feasible within the community, forcing clinicians to choose chemotherapy rather than wait for test results. Possible ways to improve this are to perform reflex testing for actionable molecular abnormalities such as EGFR-MT and ALK on metastatic NSCLC specimens and improve specimen release and tracking procedures if such testing is not performed locally, given the significant change in treatment this would allow by rapidly producing test results (16,17,25). Additionally, both resected and radically treated IIIA/B disease could also be reflex tested, allowing the use of results upon relapse. It is an historical aberration that current pathology reports detail immunohistochemical staining patterns for these metastatic biopsies, but not EGFR-MT and ALK status unless requested. Only by striving to improve the time taken for EGFR-MT testing can clinicians implement the message from EURTAC. The time for complacency and phenotypically guessing which patients will benefit from EGFR-TKI therapy has passed. It is now time for early widespread molecular testing of NSCLC patients, and time to strive for first line treatment of EGFR-MT NSCLC with an EGFR-TKI whenever possible.

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Cite this article as: Weickhardt AJ, Camidge DR, Doebele RC. A time to test, a time to treat. J Thorac Dis 2012;4(2):223-225. DOI: 10.3978/j.issn.2072-1439.2012.03.13