MOLECULAR ONCOLOGY XXX (2014) 1–30

available at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/molonc

Review

Next-generation clinical trials: Novel strategies to address the challenge of tumor molecular heterogeneity

*Daniel V.T. Catenacci**

University of Chicago Medical Center, Department of Medicine, Section of Hematology & Oncology, 5841 S. Maryland Avenue, MC2115, Chicago, IL 60637, USA

ARTICLE INFO

Article history:
Received 10 July 2014
Received in revised form
23 September 2014
Accepted 26 September 2014
Available online ■

Keywords:
Molecular heterogeneity
Inter-patient heterogeneity
Intra-patient heterogeneity
Next-generation clinical trials
Expansion Platform Designs
PANGEA
Gastric cancer
Esophagus cancer
Gastroesophageal cancer
Esophagogastric cancer

ABSTRACT

The promise of 'personalized cancer care' with therapies toward specific molecular aberrations has potential to improve outcomes. However, there is recognized heterogeneity within any given tumor-type from patient to patient (inter-patient heterogeneity), and within an individual (intra-patient heterogeneity) as demonstrated by molecular evolution through space (primary tumor to metastasis) and time (after therapy). These issues have become hurdles to advancing cancer treatment outcomes with novel molecularly targeted agents. Classic trial design paradigms are challenged by heterogeneity, as they are unable to test targeted therapeutics against low frequency genomic 'oncogenic driver' aberrations with adequate power. Usual accrual difficulties to clinical trials are exacerbated by low frequencies of any given molecular driver. To address these challenges, there is need for innovative clinical trial designs and strategies implementing novel diagnostic biomarker technologies to account for inter-patient molecular diversity and scarce tissue for analysis. Importantly, there is also need for pre-defined treatment priority algorithms given numerous aberrations commonly observed within any one individual sample. Access to multiple available therapeutic agents simultaneously is crucial. Finally intra-patient heterogeneity through time may be addressed by serial biomarker assessment at the time of tumor progression. This report discusses various 'next-generation' biomarker-driven trial designs and their potentials and limitations to tackle these recognized molecular heterogeneity challenges. Regulatory hurdles, with respect to drug and companion diagnostic development and approval, are considered. Focus is on the 'Expansion Platform Design Types I and II', the latter demonstrated with a first example, 'PANGEA: Personalized Anti-Neoplastics for Gastro-Esophageal Adenocarcinoma'. Applying integral medium-throughput genomic and proteomic assays along with a practical biomarker assessment and treatment algorithm, 'PANGEA' attempts to address the problem of heterogeneity towards successful implementation of molecularly targeted therapies.

* *Tel.*: +1 773 702 7596; fax: +1 773 702 3163.
E-mail address: dcatenac@medicine.bsd.uchicago.edu

http://dx.doi.org/10.1016/j.molonc.2014.09.011

Please cite this article in press as: Catenacci, D.V.T., Next-generation clinical trials: Novel strategies to address the challenge of tumor molecular heterogeneity, Molecular Oncology (2014), http://dx.doi.org/10.1016/j.molonc.2014.09.011

1. Targeted therapies

Clinical outcomes have significantly improved for most cancers since the introduction of classic cytotoxic agents. Cytotoxic agents can be considered 'targeted' in that they inhibit DNA synthesis and the cell division apparatus – the 'bottleneck' steps required for cancer to manifest with morbidity and mortality. (Joensuu, 2008) Some stage IV solid tumors, such as testicular cancer, even achieve long term survival with this strategy alone, while in general most advanced solid tumors derive significant palliative benefit for an increased, albeit finite, period of time. Ultimately, solid metastatic tumors develop resistance to cytotoxics, and patients succumb to their illness. A 'benefit plateau' has been reached with these cytotoxics. Off-target 'collateral damage' of normal tissues is a well-recognized potential disadvantage of cytotoxics, necessitating a delicate balance between optimizing tumor control and limiting toxicity.

Genetic aberrations identified within various tumor types, including gene mutation, gene rearrangement, and gene amplification/deletion, led to an understanding of constitutive activation of oncogenes, or loss of function of tumor suppressors, all contributing to a sequential genomic carcinogenesis model. (Fearon and Vogelstein, 1990) The ensuing concept of an 'oncogenic driver' and 'oncogene addiction' ultimately shifted the course of therapeutics development; (Weinstein and Joe, 2008; Weinstein, 2002; Vogelstein et al., 2013) the era of targeted therapies towards a putative 'Achilles heel' was born. (Dancey et al., 2012) In addition to genomic events, abnormalities of protein expression not directly a consequence of a genomic event (ie. abnormally increased protein expression in the absence of mutation, amplification, or translocation of that protein's gene) also received attention for therapeutic potential, as did key signaling 'nodes' within critical oncogenic growth and metastasis pathways. (Slamon et al., 1984; Harris et al., 1994; Islam et al., 2013; Bianco et al., 2006) Following this, pharmaceutical agents directly inhibiting the function of a 'culprit' protein could be engineered with high selectivity. (Lengauer et al., 2005) Thus, theoretically, these agents would inhibit only cancer cells possessing the dysfunctional (over-activated or over-expressed) protein, while sparing normal cells, consequently magnifying the therapeutic window. Attention to essential stromal components of tumors including immune cells, fibroblasts, and endothelial/vascular components also arose. (Devaud et al., 2013; Gimbrone et al., 1972; Kakarla et al., 2012; Bellou et al., 2013; Mueller and Fusenig, 2004; Zitvogel et al., 2006) Over the last decades, the premise of using molecularly targeted agents for targeted patient populations based on tumor/stromal molecular profiles and pathway dependencies gave rise to an array of novel drugs intended to abrogate malignant progression through these 'specific' drug–protein interactions. (Griffin, 2001; Mauro et al., 2002; Pegram and Slamon, 2000) Targets now include receptor tyrosine kinases (RTKs) (e.g. HER2, EGFR, MET), intracellular kinases (e.g. PI3K, MEK, AKT), transcription factors (e.g. STAT3), stem cell pathways (SHH/SMO, Notch), immunomodulators (e.g. CTLA4, PD1/PDL1, vaccines), and hormone receptors (e.g. estrogen, progesterone, androgen). Excluding classic cytotoxic inhibition of DNA synthesis and cell division, the main targeted therapy classes include 'biologics' (monoclonal antibodies with/without linked cytotoxics known as Antibody-Drug Conjugates (ADCs)) (Fauvel and Yasri, 2014), 'small molecules' such as tyrosine kinase inhibitors (TKIs) (Leary and Johnston, 2007; Faivre et al., 2006), and more recently, specific gene expression silencing by 'RNA interference', (Videira et al., 2014; Deng et al., 2014; Yan et al., 2014) each with their own properties, advantages and disadvantages (Table 1).

There is now significant evidence supporting the notion that cancer is driven by molecular genetic aberrations. A few well-known examples following the 'tumor→genomic driver→matched inhibitor' paradigm include: 'CML→ *BCR/ABL* translocation→imatinib', (Rowley, 1973; Druker et al., 2006; Rowley et al., 1976; Olopade, 2014) 'Breast/Gastric→*HER2* amplification→trastuzumab', (Slamon et al., 1987, 2001) 'GIST→*KIT* mutation→imatinib', (Demetri et al., 2002) and 'Melanoma→*BRAF* mutation→dabrafenib/vemurafenib'. (Flaherty et al., 2010; Chapman et al., 2011) Additionally, albeit with generally less dramatic clinical improvements, anti-angiogenesis within the stromal compartment has demonstrated benefit across solid tumor types. (Bellou et al., 2013; Shojaei, 2012) Inhibition of 'over-expressed' proteins within the tumor – in the absence of genomic aberration of that protein – has less supporting evidence in general, but has shown benefit in randomized phase II settings, such as selection of Met expressing tumors for anti-MET therapies for gastro-esophageal cancer (GEC), (Catenacci et al., 2011a; Iveson et al., 2014) or ATM expression and its potential relevance to PARP inhibition in GEC. (Bang et al., 2013) Most recently, immunomodulation including using immune checkpoint inhibitors have shown benefit in various tumor types, such as tumors expressing PDL1, (Sullivan et al., 2013; Muro et al., 2014) particularly with *concurrent* inflammatory component within the tumor-bed (Keenan et al., 2013; Le and Jaffee, 2013; June et al., 2014; Maus et al., 2014; Melero et al., 2014; Mellman et al., 2011). Based on these latter proteomic examples, 'drivers' or 'addiction' need not be considered *only* genomic necessarily; however, the more dramatic improvements in hazard ratios for survival to date are clearly the genomic driver examples (Table 2). (Iveson et al., 2014; Bang et al., 2010; Hecht et al., 2013; Ohtsu et al., 2011; Waddell et al., 2013; Lordick et al., 2013a; Ohtsu et al., 2013; Fuchs et al., 2014; Wilke et al., 2014; Satoh et al., 2014).

2. Inter-patient tumor molecular heterogeneity: the 'driver vs wheel' metaphor

As opposed to the several diverse examples above which targeted sub-populations for targeted therapy using potentially predictive biomarkers, other evaluations of novel molecularly targeted inhibitors have not been patient-selective. Among numerous examples (e.g. anti-EGFR, (Waddell et al., 2013; Lordick et al., 2013a) anti-mTOR, (Ohtsu et al., 2013) anti-Hedgehog (Cohen et al., 2013)), clinical trials for GEC based on a 'one-size-fits-all' strategy have in general been disappointing. For instance, applying an EGFR inhibitor to the entire GEC population, where genomic activation occurs in only ~5% of cases (*EGFR* gene amplification) and perhaps in another

Please cite this article in press as: Catenacci, D.V.T., Next-generation clinical trials: Novel strategies to address the challenge of tumor molecular heterogeneity, Molecular Oncology (2014), http://dx.doi.org/10.1016/j.molonc.2014.09.011