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Future Clinical Trials: Genetically Driven Trials

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SYNOPSIS

The design of modern oncology clinical trials seeks to match patients' cancer molecular biomarkers with medications that specifically target those biomarkers- a general paradigm shift in cancer care coined as "clinical cancer biology"¹. This approach exploits the synthetic lethality between a specific genetic alteration in the cancer cell and a drug: rapid termination of exaggerated kinase activity (e.g. BCR-ABL, HER2 amplification), or irrevocable DNA damage (e.g. PARP inhibitors, platinum in BRCA-mutated cancers) exemplify this phenomenon. Synthetic lethality-based investigations are driven by rapidly evolving technologies for cancer molecular profiling including not only direct testing of the tumor DNA but also blood-based biomarkers such as oncogenic metabolites and cancer specific DNA fragments in biological fluids. As these technologies evolve, future clinical trials will test drug's activity based on the molecular mechanisms, rather than by the tumor's appearance under a microscope.

Keywords

Basket clinical trial; Biomarker; Molecular profiling

Introduction

Rapid incorporation of cost- and time-efficient genomic analysis technologies has been transformative for cancer medicine. Therapy selection on part of treating physicians is progressively shifting from the empirically validated "one-size-fits-all" chemotherapy or biological agents to tailoring agents to specific molecular features of patient's tumor. It has become even more imperative to identify a drug-amenable mechanism in the setting of clinical trials selection for the patient. Again and again, studies have shown that randomly assigned treatments in patients participating in clinical trials are rarely beneficial with response rates below 5%. Contrastingly, in the "matched" scenario when a drug is given because of the existence of a mechanism defined on the basis of genetic alteration the likelihood of benefit rises to 20–30% range^{2,3}. For a physician searching for investigational therapy options, the task of deciphering the actionable cancer mechanism poses an

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DISCLOSURE STATEMENT

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unprecedented challenge previously unknown to cancer medicine. This challenge was nicely formulated by Dr. George Sledge in his 2011 ASCO presidential address as being “a clinical cancer biologist”. In this new reality, we are learning, in real time with the basic science, how cancer is a complex constellation of diseases sharing highly diverse alterations across previously incontestable organ and histological groupings and boundaries. For that reason alone, it has become more common for clinical trials to seek patients based on their tumors’ molecular signatures. As a result, molecular profiling is viewed as a critical element in the design and conduct of oncology clinical trials, as it allows investigators to match the biomarkers within an individual’s tumor with agents that specifically target those biomarkers. In the context of daily clinical practice, increasing numbers of oncologists are using molecular profiling to obtain insights into the dominant mechanism of their patients’ cancers to find appropriate anticancer therapies, either through clinical trials or through off-label use of a growing number of the FDA-approved targeted drugs. Here, we will review the successes of such matching exercises on part of clinical trials investigators, and on part of practicing clinicians whose smartness in choosing the right trial for the right patient oftentimes remains unrecognized and does not earn podium applause.

Targeting the oncogenic driver mechanism

To date, genetic characterization of most human cancers consistently revealed a high level of diversity of oncogenic mechanisms within each site of origin and histological subtype⁴⁻⁶. To complicate matters more, there is a growing appreciation of the existence of multiple genetically distinct clones within the same tumor which can compete for fitness and survival under selective pressures of anti-cancer therapies⁷. Monitoring these clonal dynamics becomes a major focus of genetic cancer surveillance which spurred rapid development of non-invasive approaches of DNA sampling from blood⁷, saliva^{8,9}, vaginal swabs¹⁰ etc. Despite the branched genetic phylogeny, some of the critical “founding” oncogenic lesions are shared between the tumor clones. In this context, molecular profiling can be used to uncover the dominant oncogenic mechanism in a tumor, and to select therapies that target the oncogenic driver¹¹. Although this approach may seem new, it dates back to 1960, when Nowell and Hungerford described the famous Philadelphia chromosome translocation *t(8,21)* activating the ABL kinase and the malignant transformation in chronic myeloid leukemia (CML)¹². Four decades later, ST1571 later known as imatinib (Gleevec), was used for the first time in humans to suppress the culprit tyrosine kinase and to reverse the cancer process clinically and biologically^{13,14}. Since the first validation of the oncogene-targeted therapy with imatinib, it has been appreciated that treating the principal driver oncogene can have a powerful impact. Experimental evidence further suggested that the rapidity of withdrawal of oncogene activity has the greatest impact on the anti-cancer effect¹⁵. This led to the proposed pulsatile blockade¹⁶, and ideas of synthetic lethality¹⁷, or combination of targeted agents¹⁸.

The ongoing trials are poised to investigate the efficacy of molecularly targeted treatments for **oncogene-defined** subsets of cancers across different tumor histologies¹⁹. In addition to the National Cancer Institute (USA) supported MATCH clinical trial, the American Society for Clinical Oncology (ASCO) launched its own TAPUR (Targeted Agent and Profiling Utilization Registry) trial offering access to the FDA-approved agents to patients with

mechanistically relevant and well-defined genetic biomarkers²⁰. These efforts require genomic pre-screening study to identify patients whose tumors harbor specific molecular abnormalities which can be matched to the relevant targeted treatments, regardless of tumor histology type. Success of these “matching” experiments is anxiously awaited. Single-institution pioneering studies² have clearly demonstrated that the unmatched cohorts of advanced cancer patients rarely benefit from these targeted therapies, while the patients with “matched” drug-to-cancer mutation do substantially better. For clinical practice, it made a random choosing of a phase I trial for patients rather unethical³. Despite the expense of finding rare patients with a desired mutation akin to searching a needle in a haystack, the rewarding successful demonstration of targeted drug’s activity motivated Pfizer to develop crizotinib, an ALK and ROS1 inhibitor for treatment of less than 5% of patients with non-small-cell lung cancer^{21–23}. Other examples abound. The tumor suppressor genes *BRCA1*, *BRCA2* and *PALB2* (partner and localizer of *BRCA2*), which are implicated in hereditary breast and ovarian cancers, also confer the extreme sensitivity to platinum and mitomycin C that has been observed in patients with pancreatic cancer^{24,25}.

Signaling redundancies, tumor clonality and escape routes

Despite similarity of biological mechanisms shared across different cancers, tissue and site of origin do exist. For instance, the success of BRAF inhibitors in V600E mutated melanoma could not be reproduced in colorectal or tumors of non-melanoma histologies carrying identical BRAF mutations^{26,27}. The phenomenon here is less likely related to difference in the BRAF biology, but rather a more rapid evolution of resistance, e.g. in colorectal cancer via EGFR signaling activation. The re-activation of the mitogen-activated protein kinase pathway is indeed universally seen in resistance to BRAF inhibitors including in BRAF V600E-mutated melanoma^{28,29}. These discoveries prompted various groups of investigators to design colorectal trials that would utilize multi-level MAPK cascade blockade with BRAF, MEK inhibitors and EGFR antibodies. The latter approach demonstrated some activity³⁰.

The example above illustrates the commonalities that clearly exist among highly diverse cancers not only in the shared mechanisms of the dominant oncogenic driver, but also in the resistance. Clonal tumor heterogeneity poses additional diagnostic and longitudinal genetic surveillance challenges to the design of clinical trials. The rate of discrepancies in HER2 status, for example in breast cancer biopsied at different time points, can be as high as around 10%³¹. Similar challenges are encountered in gastroesophageal carcinomas in which co-occurrence of HER2, EGFR and MET amplifications have been reported in the chromosomal instability subset of carcinomas⁴. Even more strikingly, under the selection pressure of a targeted agent the minority clones will become dominant. These rare clones are now being picked up with a highly sensitive deep NGS methodology such as in the case of pre-existing KRAS mutation in colorectal cancer treated with anti-EGFR antibodies³².

Rethinking the clinical trials conduct

As the National Cancer Institute launched the NCI-MATCH trial^{33–35}, an ongoing screening effort of 795 samples (according to the interim analysis at <http://ecog-acrin.org/nci-match->

easy131/interim-analysis) identified 9% mutations matching one of the 10 arms of the study. To a large extent influenced by the study drug/gene “menu”, finding the matched mutation was as likely as 18% in melanoma, brain tumors and lymphomas, 13% in colorectal and breast cancers vs. no matching in all screened so far patients with pancreatic adenocarcinoma, head and neck, endometrial, and small cell carcinoma. Other tumor types showed 2–5% matching rate. With expansion to a total of 24 arms including options for immunotherapy, FGFR1/2/3 inhibitor and palbociclib, the range of available options to match will grow significantly to the expected 23%. The lessons learned from this unprecedented exercise are set to influence the future decades of genetically tailored cancer trials and how we think of offering clinical trials opportunities to the patients. One example of the turnaround time rising from 14 days in the early months of accrual to 36 days later, as the samples flooded the sequencing labs, imposes certain restriction on who and when to be recommended to go on such trials. Nevertheless, the study succeeded in 87% of all samples completing the tumor characterization process.

The NCI-MATCH trial represents what is called a “basket trial” design: multiple arms, evolving drugs portfolio, adaptive protocol flexibility, dropout of the futile drug-gene combinations. These experiments drastically change the definition of success and target outcomes. A recent SHIVA trial (Molecularly targeted therapy based on tumour molecular profiling versus conventional therapy for advanced cancer)³⁶ used the ratio of progression-free survival (PFS) on genotype-matched treatment to PFS on genotype-unmatched treatment to assess the efficacy of therapy guided by patients’ tumor molecular profiling. This particular estimation of the clinical efficacy was used to compensate for the extreme cohort heterogeneity of tumor types. As all 195 patients were allowed to cross over upon progression, the investigators compared the algorithm-based treatment assignment with the physician’s choice. The ratio of PFS of algorithm-based treatment selection over the-physician-choice exceeded 1.3 in 37% of patients who switched to the algorithm-guided treatment arm. Contrastingly, 61% of patients who crossed over from the algorithm arm to the-physician-choice arm exceeded prior PFS by a factor of 1.3³⁶. (We are smarter than the computers, aren’t we?) The selection of PFS ratio in a pre-specified percentage of patients when comparing treatments assignment on the basis of molecular biomarkers has been first field-tested in the pivotal trial by Van Hoff et al.³⁷ In that study, which used mRNA profiling to guide chemotherapy selection, 27% of patients exceeded the PFS on their last prior therapy by a factor of 2.9, and the overall response rate was 10%.

The outcomes of these novel trials (e.g. SHIVA³⁶, Signature trial by Novartis³⁸) suggest that the lower response rates in the range of 2–4% are underestimating the clinical benefit accounted for as prolonged disease stability which translates to a greater PFS. The Signature trial is particularly worth mentioning as it utilized uniquely a patient-specific expedited IRB approval process and the site initiation process breaking the restrictive administrative thresholds. Its successful execution for the first time demonstrated the flexibility of patient-centered administration of innovative experimental therapy. We hope more examples of this approach will follow. The ASCO’s TAPUR trial (Targeted Agent and Profiling Utilization Registry) is yet another version of the molecularly-tailored therapeutic experiment as it is run essentially as a tissue-agnostic open registry of the outcomes for the currently FDA-approved agents provided through the network of participating centers²⁰. Its set primary

endpoint is the overall response rate or stable disease at 16 weeks will be prospectively evaluated at the growing number of clinical sites. The study is currently ongoing as it passed the interim futility threshold of clinical benefit in 7 out of 28 participants.

The NCI initiative to define the mechanisms of the exceptional responders^{39,40} further emphasizes the critical value of even singular clinical observations. For many patients with rare tumors or rare genetic alterations, the access to innovative therapies or even discovery of their cancer's molecular aberrations can be transformative and results to many year of life gained as we recently reported in the case of KIT-mutated neuroendocrine carcinoma⁴¹. The modern matching trials are at best covering the "druggable" cancer proteome encompassing optimistically around 10% of cancer driver mutations, while leaving the major oncogenes (RAS paralogs, MYC, beta-catenin, mutant TP53 etc.) practically unattended. We have still a long way to go to call a success.

Summary

The present era of molecularly targeted and immune therapies presents the unprecedented opportunities to transform cancer medicine to clinical cancer biology. This change is difficult and gratifying, it faces enormous regulatory, financial and administrative challenges. It redefines the clinical evidence with appreciation that each cancer is absolutely unique in its molecular makeup, clonality, patient's demographics and its perpetual evolution over time. Despite this uniqueness, common biological denominators exist and are defined, not only in the lab but also clinically, as oncogenic drivers. Impinging on these principal mechanistic elements is often successful and can be measured prospectively and retrospectively. The value of these rapidly acquired observations reshapes the regulatory and the payer policies making it easier for the patients to have access to so much needed treatment options.

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KEY POINTS

- Molecular profiling identifies distinct molecular mechanistic classes in major human cancers;
- Therapeutic successes are more likely when “matching” drugs with biologically relevant cancer mechanisms;
- Molecular profiling of cancers is an essential step in defining therapeutic strategies and clinical trials enrollment.