Cancer Clinical Trials—Do We Need a New Algorithm in the Age of Stratified Medicine?

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CANCER CLINICAL TRIALS: ADOPTING A NEW MIND SET

The explosion in genomic discovery science and its application in oncology in recent years is underpinning an unprecedented increase in our understanding of mechanisms underlying malignant processes, allowing us to identify the key molecular events that promote both the development and the evolution of a tumour in the cancer patient. However, increased understanding also creates emerging challenges, as we attempt to harness this knowledge for therapeutic benefit. Nowhere is this challenge more pertinent than in the area of cancer clinical trial development and application. Traditionally, our cancer clinical trial approach has focused on asking clinical questions and addressing these questions through clinical endpoints; we must reorient our algorithms to additionally address biological questions through biomarker-driven clinical trials with translational endpoints. Increasingly, the genetic context of the tumour is informing the clinical trial process. Greater support for publicly funded clinical trials should form part of this reengineered algorithm [1].

THE IMPORTANCE OF CLINICALLY ANNOTATED BIOSPECIMENS: TISSUE IS THE ISSUE

Discovery science is illuminating new ways that we can target the biology of cancer, focussing on particular genes, pathways and malignant processes. With our increasing aptitude for disrupting disease biology, comes the critical requirement to collect clinically annotated biological materials, both to inform our therapeutic decision-making and to assess the ability of our therapeutic approach to hit the appropriate target(s). In the past, sampling of biological material during clinical trials was considered optional or, at best, desirable; but the collection of high-quality diagnostic and serial biopsy samples, complemented with serial bio-fluids, is now a critical resource that underpins the modern clinical trial process. Next-generation sequencing and comparative genome hybridization approaches are revealing significant intratumoral heterogeneity, with subpopulations of cells harboring distinct genomic alterations within the same tumor [2], thus underpinning the absolute need for serial sampling as part of a translational clinical trials strategy.

THE TRADITIONAL MODEL FOR CANCER CLINICAL TRIALS IS UNSUSTAINABLE

Although the existing cancer clinical trial algorithm has, in the main, served us well in the past, is it still fit for purpose in the 21st century? Can we or, more pertinently, should we fund studies with 3,500 patients in each arm—comparing Potion A with Potion B—with little emphasis on disease biology? Can we justify, both at the clinical and the economic level, these large-scale trials that often generate only small incremental benefit for the cancer patient? As our discovery science reveals the complexity of cancer and its reliance on diverse biological pathways, should our therapeutic strategy not be predicated more on therapeutic approaches that block multiple pathways concomitantly, rather than the current reductionist approach of focusing on a single agent? And if we do believe in this “multiple hit” approach, how do we persuade both the pharmaceutical and regulatory communities to work with academia to pursue this more collaborative agenda? After all, do our patients not deserve an approach that delivers true transformational benefit?

But does our current clinical trial model have the capacity to undertake these translational clinical trials in the era of stratified medicine? In attempting to address this question, the international oncology community has realised that the traditional approach itself lacks flexibility, has become increasingly unwieldy, and requires a significant overhaul/restructuring to promote transformational change in the delivery of new drugs and therapies to the cancer patient. In 2010, the Institute of Medicine (IOM) published a report [3] that identified deficiencies in the National Cancer Institute (NCI) Clinical Trials Cooperative Group Program, highlighting administrative bottlenecks, delays in trial activation and completion, the paucity of innovative biomarker driven trials, and the need for increased recruitment and reimbursement of clinical trial participants. A subsequent series of workshops identified four goals to enhance clinical trial activity [4]:

1. Improve speed and efficiency of the design, launch, and conduct of clinical trials.

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2. Incorporate innovative science and trial design into cancer clinical trials.
3. Improve prioritization, selection, support, and completion of cancer clinical trials.
4. Incentivize the participation of patients and physicians in clinical trials.

CANCER CLINICAL TRIALS: RESPONDING TO THE CHALLENGES

Recognising the veracity of the findings of the IOM report, the U.S. National Cancer Institute (NCI) and the cancer community responded, with significant progress being made to increase the efficiency and productivity of the cancer clinical trials system. Key advances included (a) consolidation of the existing ten Clinical Trials Cooperative Groups into a more streamlined NCI National Clinical Trials Network (NCTN), consisting of four adult and one pediatric groups, designed to meet the first goal regarding speed and efficiency; (b) common enrollment and data management systems for all 3,100 participating community and research institutions in the Network; (c) an increased emphasis on clinical trial innovation, including the promotion of biologically focussed phase II clinical trials and the incorporation of companion diagnostics and translational science, predicated on the collection of clinically annotated bio-specimens; (d) a revamping of the clinical trials prioritisation process, and (e) a concerted promotion of increased participation in cancer clinical trials.

So, in the three years since the IOM report was published, have these structural changes led to tangible improvements that we can measure? Between 2006 and 2008, the median time to phase III clinical trial activation/commencement in the U.S. was 830 days; recent figures indicate that this has dropped to 395 days, an impressive 52% reduction [5]. The situation for phase II clinical trials has also improved, with a 31% reduction in time from concept to commencement.

In Europe, we need to radically overhaul our structures and move to a level at which discovery science is appropriately resourced, innovation is supported—not hampered, and

translational science is embedded—not optional. As there is no European equivalent to the NCI, the EORTC serves in part as one of the very few pan-European research groups. Nevertheless, the current European Clinical Trials Directive has failed to harmonize and standardize the procedures for clinical trial approval and conduct; in addition, central infrastructural funding is lacking. It is critical that the ongoing revision of this European Clinical Trials Directive [6] will ensure a more effective clinical trial activity; otherwise, cancer clinical trials and translational research activity in Europe will be severely compromised.

PLOTTING THE PATHWAY TO SUCCESS

Proof of mechanism trials that test new therapeutic entities in small groups of patients are increasingly being used to demonstrate both molecular and clinical efficacy. These “nimble” trials, utilising genomic profiling for eligibility and incorporating translational endpoints, have the capacity to rapidly validate promising agents with true therapeutic potential; they also allow us to dismiss the “losers” at an earlier stage, thus allowing precious resources to be channelled towards the potential “winners”, providing them with the best opportunity to succeed. Increasingly, the concept of “basket trials”, by which biomarker stratification allows simultaneous single-arm targeting of multiple alterations in diverse signalling pathways, is being embraced by the international oncology community.

Creating an innovative global cooperative cancer clinical trial culture that recognizes and encourages the diverse but complementary contribution from all stakeholders will underpin a meaningful translation of discovery science to clinical benefit. We should be competing against our common enemy—cancer—rather than against each other.

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EDITOR'S NOTE: Accompanying this article is an online video roundtable (http://sto-online.org/european_perspectives) in which the authors discuss and debate the key issues that cancer clinical trials must address in the 21st century.