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Editorial

Rethinking clinical trials

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Introduction

Historically clinical trials have been used to establish standard of care and in general advance treatment options of oncology patients. However, has the practice of incorporating these results into actual patient care, kept pace with advances occurring simultaneously in biology, genomics and imaging modalities? Breast cancer trials serve as a good example in that the early trials establishing the benefit of radiation in breast conservation occurred during a time when the imaging modalities were crude by modern day standards and the use of targeted systemic therapies was not in place. The true benefit of adjuvant radiation may evaporate in time but is unlikely to be a focus of future trials.

Often trials are not completed as per study design and when incorporated into clinical practice do not consider the original study population. An example would be the American College of Surgeons Oncology Group Trial (ACOSOG) Z0011 whose aim was to evaluate the impact of an axillary node dissection on local regional control and on survival in early stage breast cancer patients managed by breast conserving surgery. A specific goal of the study was to determine if axillary lymph node completion dissection could be safely omitted if the sentinel lymph node contained metastatic disease. The trial was activated in 1999 with a target accrual of 1,900 patients. The trial did not met targeted enrollment and closed in 2004 with 891 patients enrolled. Although eligibility criteria included patients over the age of 18, approximately two-thirds were over the age of 50. The study also had a low event rate, included women with favorable small ER+ tumors with the majority invasive ductal carcinoma. The accrual target of 1,900 was based on an estimate of 500 deaths for the trial to reach 90% power. Even if the trial enrolled the target number it would have taken 20 years of follow up due to the unanticipated lower event rate. Therefore the findings were determined to be non-inferior and readily incorporated into patient care. The findings were extrapolated to younger women, those with ER- tumors as well as lobular cancers all of which were underrepresented in the study population[1].

Clinical trials that test combinations of therapies are designed to identify optimal treatment approach with the goal of improvement in patient outcome for the general populace. But these trials are often challenged by bias of patient enrollment. That is they mostly include patients with lower risk profiles for disease recurrence and have less in the way of co-morbidities than the average patient population. Often the enrolled participants do not represent diversity of the cancer patient population in regards to race and socioeconomic background. Likewise heterogeneity of the tumor itself exists when considering the genetic composition and variables of the disease. Yet findings from these biases are incorporated into treatment management based upon the magnitude of treatment effect without considering if credible in translation based upon eligibility criteria for enrollment.

The National Cancer Institute (NCI) has addressed some of these concerns through the Experimental Therapeutics Clinical Trials Network (ETCTN). These teams of investigators will formulate proposals for early stage clinical trials based on the molecular targets of the drugs or class of drugs to be tested. These trials seek to enroll patients based on the molecular composition of their tumors[2].

Should we be in fact considering the "n-of-1" strategy for clinical investigation? These single subject trials consider efficacy and side-effect profiles of unique interventions. Targeted individualized therapy is the goal using objective data-driven criteria[3]. These trials have the potential to truly change the management of a cancer patient with the merger of evidence based medicine and individualized therapy while considering the balance of the patient's characteristics and the tumor's profile. It may in fact offer the truest form of cost effective medicine.

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