Two Drugs Versus One Drug in Non–Small-Cell Lung Cancer: Are We Asking the Right Questions?

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The treatment of oncologic diseases has evolved after decades of exhaustive, time-consuming, expensive, and frequently inefficient trial and error. With a limited arsenal of therapeutics, basic questions regarding the dose, schedule, and optimal combination of therapeutics dominated the research landscape for many years. Throughout the 20th century, cancer-drug discovery had largely occurred through serendipitous events; chief among these events included the observations of the effects of mustard gas on soldiers during World War I, the effects of folate and plant products on the growth of leukemic cells, and the death of bacterial cells in a water basin exposed to electrodes made of platinum. These observations were followed by years later by a greater understanding of the mechanisms that caused this cancer-kill effect. Several key principles of treatment emerged from the successful treatment of acute leukemia that would be tested over and over again for the next four decades, namely, the most effective treatment for cancer would come from the combination of drugs that had a single-agent activity, differing mechanisms of action, nonoverlapping toxicities, evidence of preclinical synergy, and the ability to give each agent in its full dosage.

On the basis of the spectacular success seen in acute leukemia, non-Hodgkin lymphoma, and testicular cancer in the 1970s and 1980s, this paradigm appeared to be a logical one to conquer all cancers. The war over cancer would be won by inhibiting DNA synthesis and/or poisoning the mitotic spindle in cancer cells and/or inhibiting other cellular processes while repairing those functions in normal tissues. As a result, the oncologic literature is densely populated with thousands of clinical trials that have tested the manipulations of dose and schedule of platinum agents, antifolates, mitotic spindle poisons, and alkylating agents in nearly every disease and nearly every combination.

Without the luxury of understanding the molecular differences between cancers and the tremendous limitations of this approach in most diseases, researchers attempted to answer simple questions, including the value of combination versus single agent therapy. In the article that accompanies this editorial, Ardizzoni et al\(^1\) randomly assigned patients previously treated with a platinum-based first-line regimen for stage IIIIB or IV non–small-cell lung cancer to receive pemetrexed with or without carboplatin as a second-line therapy. The design used standard inclusion and exclusion criteria and end points. The alternate hypothesis was that the combination of carboplatin and pemetrexed would improve progression-free survival (PFS) to 4.5 from 3 months with pemetrexed alone. The sample size required 230 patients to demonstrate this modest improvement in PFS with these modestly active drugs. The authors reported no improvement in overall survival, even when enlarging their sample size by combining their data with that of the NVALT7 trial (Nederlandse Vereniging Artsen voor Longziekten en Tuberculose Lung Cancer Group Trial 7) of a similar design. Minor differences noted in the response rate and PFS between the studies was likely attributed to differing patient and disease characteristics reported in these studies. One interesting observation from the study by Ardizzoni et al\(^1\) was the improved survival for patients with squamous cell treated with carboplatin and pemetrexed compared with pemetrexed alone. Because pemetrexed is believed to have minimal activity in squamous-cell lung cancers, does this signal a rationale for using carboplatin alone in this setting? Because of the spoils of testable hypotheses today, it is doubtful that this question will or should be answered in a separate clinical trial.

The question of one drug versus two drugs has been previously evaluated in a meta-analysis by Di Maio et al\(^2\) In this analysis, response rates and PFS were improved with two drugs compared with one drug, but survival was not prolonged, and toxicity was increased with the combination. Do we need additional studies of this nature? In a time of substantial scientific advances, are we still asking the right questions? At the time the trial by Ardizzoni et al\(^1\) was conceived, my answer would have been yes. In 2012, the answer is no.

Our understanding of lung cancer has markedly advanced since the conception of the trial by Ardizzoni et al\(^1\). Lung cancer is no longer only thought of as small-cell lung cancer, in which chemotherapy and radiation have substantial benefits, albeit short-lived in most patients, and non–small-cell lung cancer, in which chemotherapy and radiation have modest benefits. We must now think of non–small-cell lung cancer as non–squamous non–small-cell or squamous cell lung cancer. We must consider several issues including whether patients are bevacizumab eligible, their smoking history, and the presence of molecular abnormalities such as an EGFR mutation, ALK gene rearrangement, ROS-1 gene rearrangement, or KRAS mutation. Should we give patients maintenance therapy, and if so, will it be switch maintenance, whereby we change to a different drug before disease progression in patients receiving first-line therapy, or continuation maintenance, whereby we continue one or more drugs given in the first-line therapy until disease progression or intolerable adverse effects? These are the
key clinical questions that must be addressed for patients with advanced non–small-cell lung cancer. Each of these questions has had a major effect on the approach to treatment-naive patients with stage IV lung cancer. Although we continue to debate the preferred approach for patients with each of these scenarios in the first-line setting, it is clear that the answers to these questions will have an effect on our choices for second-line therapy. We must also contemplate additional variables such as whether the molecular status at diagnosis has an effect on what we do for second-line treatment. Does the molecular status at baseline even reflect the current status of disease? Who should get a repeat biopsy at the time of disease progression? With a plethora of new targets and targeted agents, researchers are designing trials that are not asking whether one drug versus two drugs should be used or how much should be used but, rather, which drug for which patient should be used. For example, Tsimberidou et al matched patients with molecularly targeted phase I trials on the basis of the gene mutations from the tumors of the patients. Forty patients with identified molecular targets received target-specific phase I drugs. The remaining patients were empirically treated with a phase I drug that they were eligible to take. Response rates were 27% versus 5% for the target-matched patients and empirically treated patients, respectively.

The 21st century has brought us the molecular era of oncology followed closely by the genomic era. The lessons of the 20th century include the failure to realize substantive gains in many cancers by using the old paradigm. At the forefront of these failures is the management of metastatic non–small-cell lung cancer. The rapidity at which the fundamental shift in focus and priorities to test the new models of the molecular and genomic eras has occurred is stunning. The understanding of the molecular underpinnings of non–small-cell lung cancer has brought hope and more successful treatment, including the discovery of epidermal growth factor receptor tyrosine kinase inhibitors for patients with EGFR mutations and anaplastic lymphoma kinase inhibitors for patients with ALK gene rearrangements. For these patients, gains in survival are not measured in weeks or months but, in some cases, years. History teaches us that substantial gains in the treatment of non–small-cell lung cancer will not come from minor manipulations in dose, schedule, and sequencing of these newer agents, just as it has not for classic chemotherapy drugs. As the saying goes, those that do not know their history are destined to repeat it.

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