

COUNTERPOINTS

Current Controversies in Hematology and Oncology

Targeted Therapy vs Chemotherapy: Which Has Had More Impact on Survival in Lung Cancer?

Chemotherapy and targeted therapy both have earned their place in the treatment of lung cancer, but which has made the larger contribution? In this month's Counterpoints section, Dr D. Ross Camidge of the University of Colorado Comprehensive Cancer Center makes the case for targeted therapy, whereas Dr Mark A. Socinski of the University of Pittsburgh Medical Center makes the case for chemotherapy.

Does Targeted Therapy Make Patients Live Longer? Hard to Prove, But Impossible to Ignore



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Initially, targeted therapy was not a huge breakthrough in the treatment of advanced non-small cell lung cancer (NSCLC). For example, when the US Food and Drug Administration (FDA) first approved the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) erlotinib (Tarceva, Genentech/Astellas) in 2004 for second- or third-line unselected advanced NSCLC, it had been shown to improve overall survival (OS) from 4.7 to 6.7 months—a modest gain.¹ What has sparked the lung cancer treatment revolution is the use of targeted therapies in combination with specific predictive biomarkers.

Undeniable Successes for PFS and Response Rate

It was the postlicensing exploration of somatic (tumoral) *EGFR* mutations as effective predictive biomarkers for EGFR TKI benefit that began the rapidly accelerating destruction of the one-size-fits-all model of lung cancer care. Though erlotinib initially produced a median progression-free survival (PFS) of 2.2 months and an

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The Significant Impact of Chemotherapy in Lung Cancer



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The reality of lung cancer treatment in clinical practice is caring for patients with advanced-stage disease. The median age of patients is approximately 70 years, and the list of comorbidities usually is extensive owing to the predominance of past or current smoking in this patient population.

The vast majority of people with lung cancer have NSCLC. We have learned that this population harbors a myriad of molecular alterations, and ranks as one of the top malignancies in that respect. We also have learned that a growing list of targetable oncogenic drivers underlies the pathogenesis of disease in a proportion of lung cancer patients who are never smokers or former light smokers. These patients tend to have a lower level of “molecular mayhem” than those who are smokers.

The use of targeted therapies in patients with oncogenic drivers has been one of the recent success stories in oncology, leading to a heightened level of enthusiasm for the discovery and development of novel targets and therapies. It is my belief that the impact of chemotherapy needs to be considered separately in these 2 distinct

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Does Targeted Therapy Make Patients Live Longer? Hard to Prove, But Impossible to Ignore (cont)

objective response rate (ORR) of 8.9% in the National Cancer Institute of Canada Clinical Trials Group Study BR.21 cited earlier, the same drug at the same dose given to patients preselected for having an activating *EGFR* mutation produced a PFS of 14 months and an ORR of 70.6%.^{1,2} Similarly impressive values also have been seen when the anaplastic lymphoma kinase (ALK) inhibitor crizotinib (Xalkori, Pfizer) is given to those proven to have an *ALK* rearrangement in their lung cancer: one study found a PFS of 9.7 months and an ORR of 60.8%.³

Multiple phase 3 studies in both the advanced *EGFR* mutated and *ALK* rearranged NSCLC populations show the benefit of targeting an oncogenic driver vs standard first- or second-line chemotherapy.⁴⁻⁷ Given that the PFS benefit from the targeted therapy in these trials (range, 3.9-4.5 months) is longer than the historical OS benefit seen with either first-line platinum-based chemotherapy (1.5 months) or second-line docetaxel (2.4 months) in the general lung cancer population, it may seem as if everyone could agree that targeted therapy was the clear winner in terms of its impact on survival in lung cancer.^{8,9} Yet, arguments in favor of chemotherapy still can be raised.

The Immediate vs Later Survival Benefit Conundrum

The biggest argument for chemotherapy's superior effect on survival in lung cancer comes from the failure of all of the phase 3 studies of *EGFR* TKIs vs chemotherapy to show an OS advantage.^{4,5,10-14} Given the presence of significant and unequivocal immediate-term (ORR and PFS) benefit, there are only 2 possible explanations for this.

The first explanation is that the OS benefit exists, but the difference is somehow being reduced within the trial population because of the impact of subsequent active therapies. This could reflect true imbalances in therapy, such as more off-study crossover in the control arm to agents targeting the same pathway, and/or the fact that survival with access to active therapies in both arms is so prolonged that the impact of a few months of differential exposure within the trial becomes insignificant. The hypothesis that salvage therapy after progression hides true OS benefit is supported by 3 circumstantial lines of evidence:

(1) The extent of survival benefit, although small and not statistically significant, trends toward a greater effect earlier in development of each drug class, when fewer opportunities for crossover exist. Certainly, the nonsig-

nificant hazard ratio (HR) for OS in the subset of patients with mutated *EGFR* retrospectively identified within the BR.21 study (the first phase 3 study conducted before an *EGFR* TKI was licensed) is noticeably lower (HR, 0.55; 95% CI, 0.25 to 1.19; $P=.12$) than the nonsignificant HRs in, for example, the later phase 3 trials of EURTAC (European Erlotinib Versus Chemotherapy; HR, 1.04; 95% CI, 0.65-1.68; $P=.87$) and OPTIMAL (HR, 1.04; 95% CI, 0.69-1.58; $P=.69$).^{4,14,15}

(2) Combining data across trials increases the power of the data set to reveal small OS effects despite the effect of salvage therapies. At the 2014 annual meeting of the American Society of Clinical Oncology, this was shown for the first time looking across 2 first-line phase 3 trials of afatinib (Gilotrif, Boehringer Ingelheim) in patients with *EGFR* mutations vs either cisplatin-pemetrexed (LUX-

Key subsets of patients are now living longer than they did before targeted therapies were available.

Lung 3) or cisplatin-gemcitabine (LUX-Lung 6).¹⁶ The updated OS advantages for afatinib in LUX-Lung 3 and LUX-Lung 6 were both nonsignificant when analyzed separately (HR, 0.88; $P=.3850$ and HR, 0.93; $P=.6137$, respectively). When the data were combined, however, OS became statistically significant, with the benefit being most marked among those patients with an *EGFR* exon 19 deletion (HR, 0.59; 95% CI, 0.45-0.77; $P=.0001$).

(3) Outside of clinical trials, the life expectancy of patients with these abnormalities is increasing. Unfortunately, we do not yet have good national databases of patients with *EGFR* mutations and *ALK* rearrangements. However, we have seen from retrospective analyses of patients with *ALK* rearrangements that OS was significantly longer among those who got crizotinib compared with those who died before getting access to the drug in clinical trials (HR, 0.36; 95% CI, 0.17-0.75; $P=.004$).¹⁷ Similar supporting evidence comes from the recognition that *EGFR* mutations are more common among patients with certain characteristics, such as Asian heritage. Consequently, consistent with a true effect of *EGFR*-targeted

therapy on survival in patients with *EGFR* mutations, the 12-month survival rate has increased more dramatically among Asians than among white and African American patients with NSCLC in recent years.¹⁸ Finally, although there has been a recent fall in the US incidence of lung cancer starting in approximately 2005, the prevalence has subtly increased consistent with an overall improvement in survival in the NSCLC population.¹⁸ Although this could reflect many advances, it is striking that the largest increase in incidence occurred from 2005 to 2006, soon after the widespread introduction of *EGFR* TKIs.

If none of these 3 lines of evidence are true, the only alternative explanation is that after dramatic improvement in PFS and ORR from TKI exposure, the prognosis is somehow later worsened and all the initial benefit evaporates after progression. In other words, the targeted drug does nothing more than redistribute the available total time alive, sequestering it into the period when the patient is first on the targeted therapy and removing it from the period after disease progression. Although “flare” reactions from the reemergence of previously suppressed clones when an active targeted therapy is discontinued are well recognized, it is hard to imagine that these could truly eat up a PFS benefit of several months.¹⁹

Is Targeted Therapy Only For a Niche Population?

The other major argument made in favor of chemotherapy’s survival impact tends to focus on chemotherapy being inferior to targeted therapy but still having an overall greater effect on survival because of the perceived rarity of some of the actionable molecular subtypes of lung cancer. In other words, chemotherapy may not be as effective as an *EGFR* TKI in a patient with an *EGFR* mutation, but chemotherapy works in everyone and not just some rare subgroup. However, there are major problems with this logic.

First, there are significant variations in the frequency of actionable biomarkers around the world. Although *EGFR* mutations may be present in only 10% to 20% of lung cancer patients in the West, they exist in up to 60% of patients in East Asia.²⁰ Second, although there are plenty of targeted therapies still in need of a good predictive biomarker, the list of well-defined molecular abnormalities with proven benefit from a targeted drug continues to grow and it is the sum of these subtypes, not their individual frequencies, that is important.²¹⁻²⁴ With the increased use of multiplexed molecular assay platforms, many of these rare subtypes routinely are being revealed and can add up to a significant fraction of NSCLC with a targetable abnormality.

Of course, despite our best efforts, many NSCLC patients, particularly those with nonadenocarcinoma histologies, will remain without an actionable oncogenic

driver. Yet this is not an argument in favor of chemotherapy as a panacea. The fact that we do not have a good biomarker for who will benefit from chemotherapy does not mean that chemotherapy works in everyone, or even that it works in those without an actionable molecular marker. Given that several oncogene-addicted subtypes of NSCLC may be particularly sensitive to chemotherapy (eg, carboplatin and paclitaxel for patients with *EGFR* mutations, and pemetrexed for patients with *ALK* rearrangements), the true benefit of chemotherapy in “pan-negative” patients may be even lower than our traditional unselected population data suggest. That is, the benefit of chemotherapy might be reduced if we could retrospectively remove these patients from the historical data set of chemotherapy trials.^{13,25}

Summary

Over the last few years, the use of molecular profiling to direct patients to specific targeted therapies has irrevocably changed how we treat lung cancer. Despite this, many randomized trials have failed to show an apparent survival advantage from this approach in stage IV disease. Are we using targeted therapy for no real benefit, lulled into a false sense of security by impressive radiographic responses—only to shorten the patient’s life later? Of course not, as anyone who treats lung cancer patients can tell by how the quality and quantity of our patients’ lives have improved in the last few years. Profound and durable responses now can be achieved in an increasing proportion of patients across a range of actionable abnormalities; historical trends and meta-analyses of trials all suggest the overall survival benefit is really there; and, when large populations are explored, key subsets of patients, who are likely to be the ones harboring the most actionable molecular markers, are now living longer than they did before targeted therapies were available. Is it easy to point to a single irrefutable piece of evidence proving the survival benefit of targeted therapy in lung cancer? No, but it is also impossible to ignore.

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The Significant Impact of Chemotherapy in Lung Cancer (cont)

populations: the relatively small number of patients with targetable, advanced-stage disease, and everyone else.

Data on the Use of Chemotherapy in Lung Cancer

Cytotoxic chemotherapy got off to a bad start in lung cancer. Initial trials evaluating alkylating agents¹ suggested that therapy actually shortened survival compared with best supportive care (BSC).

It was not until the development of cisplatin in the late 1970s that evidence evolved suggesting that chemotherapy was having a positive effect on outcomes in people with lung cancer. The first major development occurred when the NSCLC Collaborative Group published a meta-analysis in 1995 that evaluated the impact of cisplatin-based chemotherapy on NSCLC. This study, which included 8 trials (778 patients) comparing cisplatin-based combinations with BSC, showed a modest yet statistically and clinically significant survival benefit from cisplatin in advanced-stage NSCLC. The absolute difference in median survival times was 2 months (6.7 vs 4.7 months), resulting in a 10% improvement in the 1-year survival rate. The HR for the effect of chemotherapy was 0.73 ($P < .0001$), showing a 27% risk reduction in death compared with BSC.

Over the following decade, randomized clinical trials addressed the number of cytotoxic agents (1 vs 2 vs 3), platinum- vs nonplatinum-based regimens, and duration of therapy in order to arrive at our current standard of administering a platinum-based doublet for 4 to 6 cycles. Histology became a factor in choosing the appropriate doublet when cisplatin-pemetrexed was shown to be less effective than cisplatin-gemcitabine in patients with squamous histology. Additionally, cisplatin-pemetrexed had a survival advantage compared with cisplatin-gemcitabine in patients with nonsquamous histology.

A second major development regarding cytotoxic chemotherapy was the demonstration that docetaxel improved survival compared with BSC following previous exposure to platinum-based therapy.² This trial was followed by a randomized phase 3 trial comparing docetaxel with pemetrexed that showed essentially identical response rates, PFS rates, and OS rates.³ These trials ushered in the era of second-line therapy in advanced NSCLC. A recent report assessing the use of both first-line and second-line chemotherapy over a 10-year period from 1997 to 2007 showed increasing percentages of patients receiving multiple lines of therapy over that time.⁴ This was associated

with an increased survival rate over that period that the authors attributed to the use of chemotherapy, which was shown to improve survival compared with BSC.

The third major development was the demonstration that maintenance chemotherapy improved survival compared with placebo. The best evidence for this is a trial of pemetrexed switch maintenance by Ciuleanu and colleagues⁵ and another trial of immediate vs delayed docetaxel by Fidias and colleagues.⁶ Although this approach was dubbed “maintenance therapy,” these trials evaluated the use of FDA-approved second-line agents following 4 cycles of first-line platinum-doublets in patients whose disease was either responding or stable (nonprogressing). The lesson from these trials was that exposure to active second-line chemotherapy agents improved survival because patients randomized to the control arms of these trials (placebo in the case of pemetrexed⁵ and delayed

The impact of chemotherapy is clinically as well as statistically significant.

docetaxel in the Fidias trial⁶) more often received effective second-line therapy. The concept that more frequent delivery of effective chemotherapy can improve survival is supported by the study recently reported by Ho and colleagues⁴ that is discussed above.

The Current Molecular Era

The trials assessing the impact of chemotherapy in advanced NSCLC largely were done prior to the current molecular era. It is true that certain molecular subsets of patients—those with *EGFR* mutations and *ALK* translocations—seem to have more sensitivity to certain chemotherapy agents or combinations. It is impossible to know what influence these subsets might have had on the results from trials done decades ago and nobody would advocate doing a trial of chemotherapy vs BSC in true wild-type populations in this era. We do have evidence from recent trials that targeted therapy can improve survival compared with chemotherapy in patients with *EGFR* mutations. In certain molecular subsets where the pathogenesis of the disease is

clearly driven by a particular oncogene, it is not surprising that targeting the oncogenic driver results in better survival outcomes. Although our standard chemotherapy agents all have targets, these are largely limited to DNA replication and the mitotic apparatus and are less “elegant” than newer targets, particularly given our modern day understanding of the molecular basis of lung cancer.

A Modest But Significant Effect

The impact of chemotherapy is modest no matter what line of therapy you consider, but it is clinically as well as statistically significant. In general, the relative reduction in death over time is approximately 20% to 30%. One could make a very cogent argument that a 20% to 30% risk reduction imposed over several lines of therapy is clearly a clinically meaningful strategy. One issue in this disease is the percentage of patients treated in the first-, second-, and third-line setting. Recent studies have suggested that fewer than 50% of patients are treated in the first-line setting, and the drop-off from first- to second-line treatment is approximately 30% to 40%.^{7,8} The reasons for these numbers are complex; the fact that this disease historically has been shrouded in therapeutic nihilism contributes to these phenomena.

Lastly, one must not forget that chemotherapy has been integrated into the treatment of the earlier stages of NSCLC. Adjuvant platinum-based chemotherapy in resected stage II/III NSCLC (and possibly certain subsets of stage I) clearly has a survival advantage over surgery alone.⁹ Combination chemoradiation in unresectable stage III NSCLC also leads to improvement in overall survival compared with radiation alone.¹⁰ These paradigms have been established by decades of clinical trials that have systematically evaluated the role of chemotherapy in these settings. The integration of platinum-based chemotherapy into the surgical and radiation arenas would not have been possible without establishing its role in advanced NSCLC.

Currently, the only information we have on targeted agents is in targeted populations (defined by biomarkers such as *EGFR* mutations and *ALK* translocations) with advanced disease. These patients represent fewer than 15% of the NSCLC population, and the advances we have made in these selected patients have been demonstrated only in the stage IV setting.

Chemotherapy has made a difference, albeit a modest one, across all patients and all stages of this disease and is here to stay for the foreseeable future.

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“Counterpoints” is a section in *Clinical Advances in Hematology & Oncology* in which we address clinical controversies and other questions of importance to oncologists and hematologists. We feature between 2 and 8 panelists for each question.

What topics would you like to see addressed in future issues? Please send your ideas to editor@clinicaladvances.com.