5 Minute JournalClub

Key ASCO Presentations
Issue 7, 2010

Carboplatin and Paclitaxel as Therapy for Elderly Patients with Advanced Non-Small Cell Lung Cancer (NSCLC)

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CME INFORMATION

OVERVIEW OF ACTIVITY

Each year, thousands of clinicians and basic scientists sojourn to the American Society of Clinical Oncology (ASCO) Annual Meeting to learn about recent clinical advances that yield alterations in state-of-the-art management for all tumor types. Attracting tens of thousands of attendees from every corner of the globe to both unveil and digest the latest research, ASCO is unmatched in attendance and clinical relevance. Results presented from ongoing trials lead to the emergence of new therapeutic agents and changes in the indications for existing treatments across all cancer medicine. Despite the importance of the conference, the demands of routine practice often limit the amount of time oncology clinicians can realistically dedicate to travel and learning. To bridge the gap between research and patient care, this CME activity will deliver a serial review of the key presentations from the ASCO Annual Meeting and expert perspectives on how these new evidence-based concepts can be applied to routine clinical care. This activity will assist medical oncologists and other cancer clinicians in the formulation of optimal clinical management strategies for patients with diverse forms of cancer.

LEARNING OBJECTIVE

- Integrate new clinical trial evidence demonstrating the efficacy and safety of combination chemotherapy with paclitaxel/carboplatin into the therapeutic algorithm for elderly patients with advanced NSCLC.

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FACULTY — The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:

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Key ASCO Presentations
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To go directly to the slides and commentary, **click here**.

Last Friday we hosted our annual daylong lung cancer Think Tank with seven renowned investigators, co-chaired by Tom Lynch (be on the lookout for the highlights audio program). One of the main objectives of this closed "recording session" was to review data sets from Chicago, and this dizzying scientific chat included discussion of the following work profiled in the enclosed slide sets:

1. **Crizotinib in patients with EML4-ALK mutations**
An update of the stunning Phase I-II data first presented at ASCO '09 included impressive waterfall plots in which almost all patients had reduced tumor sizes with this not-yet available agent. Approximately four to five percent of patients harbor this newly described translocation that fits the classic oncogene addiction model, and at the Think Tank Dr Lynch described one such individual from his practice who entered this study with substantial symptomatic tumor burden and is still in response two years later. All in attendance agreed on the urgency of making this agent available and of standardizing and disseminating the assay technology, but the faculty was unsure how long this will actually take.

2. **EGFR TKIs versus chemotherapy for patients with EGFR mutations**
A CALGB trial in first-line *metastatic* disease reinforced recent study results clearly demonstrating that a TKI without chemo is preferred for these patients. In contrast, the confusing and incomplete **BR19 trial** suggested the possibility that in the *adjuvant* setting, not only would EGFR TKIs not be beneficial, but for very much unknown reasons they could also be detrimental. Specifically because of this and one prior Stage III data set, there was a strong sentiment among the Think Tank investigators not to use these agents as adjuvant therapy outside a protocol setting.

By the end of this amazing day, it was apparent that a new tissue-based algorithm for systemic treatment of advanced non-small cell lung cancer was on the table. Specifically, the faculty endorsed the baseline evaluation for patients with adequate tumor specimens for EGFR and EML4-ALK mutations and maybe K-ras, which might be predictive of benefit with sorafenib. For patients with needle biopsies without the necessary tumor quantity to conduct these assays, the decision regarding rebiopsy must be individualized based on smoking history, site of disease and performance status. Ed Kim, who first reported his landmark "BATTLE" trial at AACR — followed by

more data from Roy Herbst at ASCO — cautioned that core biopsies by interventional radiology are much more likely to yield adequate tissue than those obtained by bronchoscopy. After hearing MD Anderson coinvestigator John Heymach comment on the unprecedented translational data in BATTLE, it was clear this was the future paradigm of lung cancer research.

3. **Palliative (supportive) care extends survival in the advanced disease setting**
In what some view as the biggest surprise of ASCO, a Harvard randomized trial demonstrated marked OS increases for patients who visited a palliative care specialist about once a month. Dr Lynch had a number of patients in this study and believes the benefits were primarily the result of better management of depression, anxiety and "existential angst." All agreed that "If this was a drug, we'd use it." How to get this advance to patients is unclear.

4. **Older patients may benefit from doublet chemotherapy in first-line advanced disease**
This **plenary presentation** confirmed an emerging theme within oncology: Older patients who can safely tolerate standard therapy derive the same benefits as younger patients.

Next up on our final ASCO issue of 5-Minute Journal Club: GI cancers and a provocative study in pancreatic cancer.

Neil Love, MD
Research To Practice
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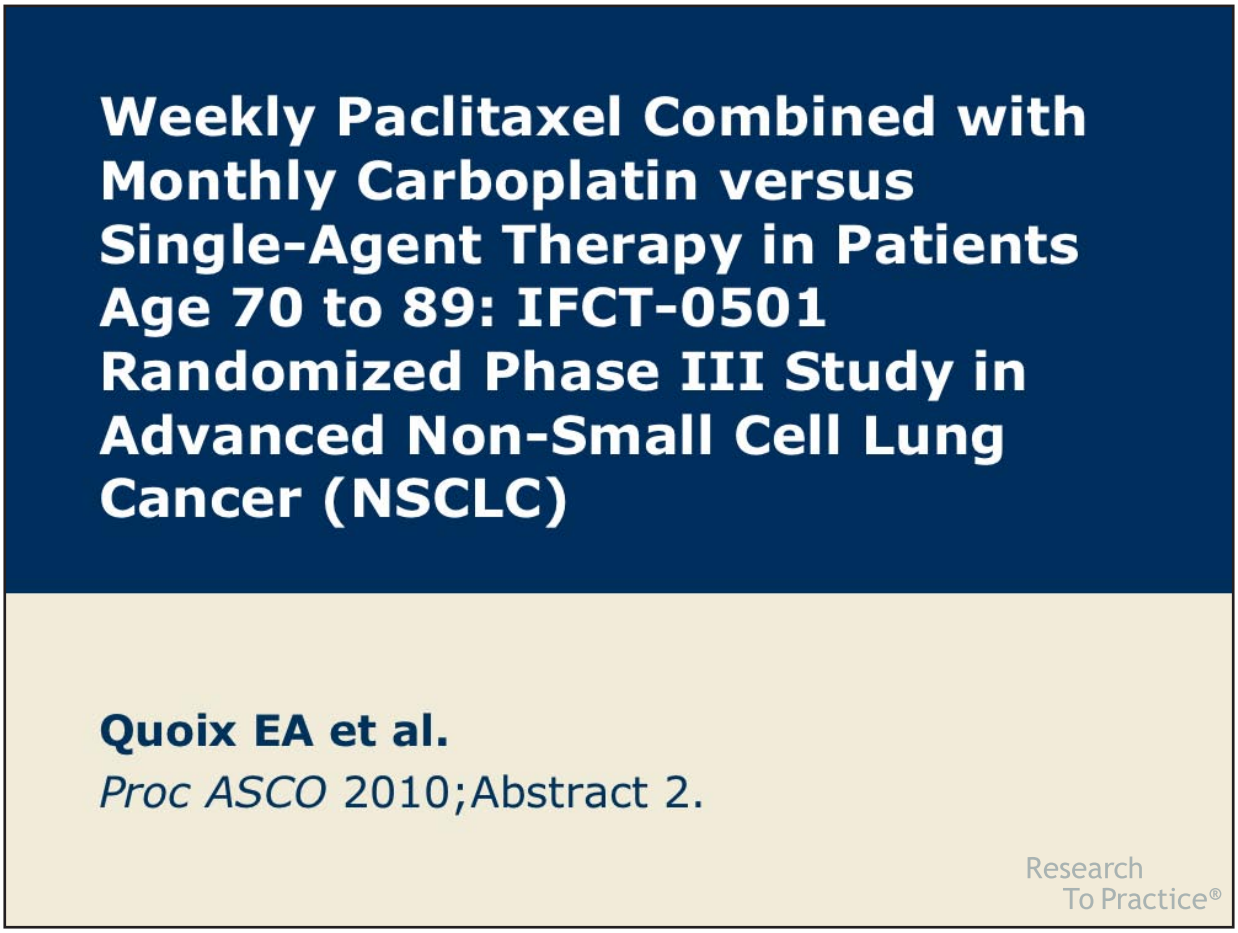
Carboplatin and Paclitaxel as Therapy for Elderly Patients with Advanced Non-Small Cell Lung Cancer (NSCLC)

Presentation discussed in this issue

Quoix EA et al. **Weekly paclitaxel combined with monthly carboplatin versus single-agent therapy in patients age 70 to 89: IFCT-0501 randomized phase III study in advanced non-small cell lung cancer (NSCLC).** *Proc ASCO* 2010;**Abstract 2**.

Slides from a presentation at ASCO 2010 and transcribed comments from recent interviews with F Anthony Greco, MD (6/15/10), Roy S Herbst, MD, PhD (6/23/10) and Corey J Langer, MD (7/2/10)



Introduction

- Incidence of advanced NSCLC in the elderly is increasing, with increased life expectancy and increased incidence of cancers with aging.
- Phase II trial in elderly patients with advanced NSCLC showed gemcitabine to be effective (*Lung Cancer* 2005;47:405).
  - Objective response rate (ORR) was 28.2% and median survival was 6.83 mo.
- Phase II study in elderly patients with advanced NSCLC showed carboplatin plus paclitaxel to be effective (RR 43%, MST 13.6 months) and well tolerated (*J Thorac Oncol* 2006;1:328).
- **Current study objective:**
  - Phase III trial to compare efficacy and tolerability of gemcitabine (gem) or vinorelbine (vin) monotherapy to carboplatin/paclitaxel in elderly patients with advanced NSCLC.

Quoix EA et al. *Proc ASCO* 2010;Abstract 2.

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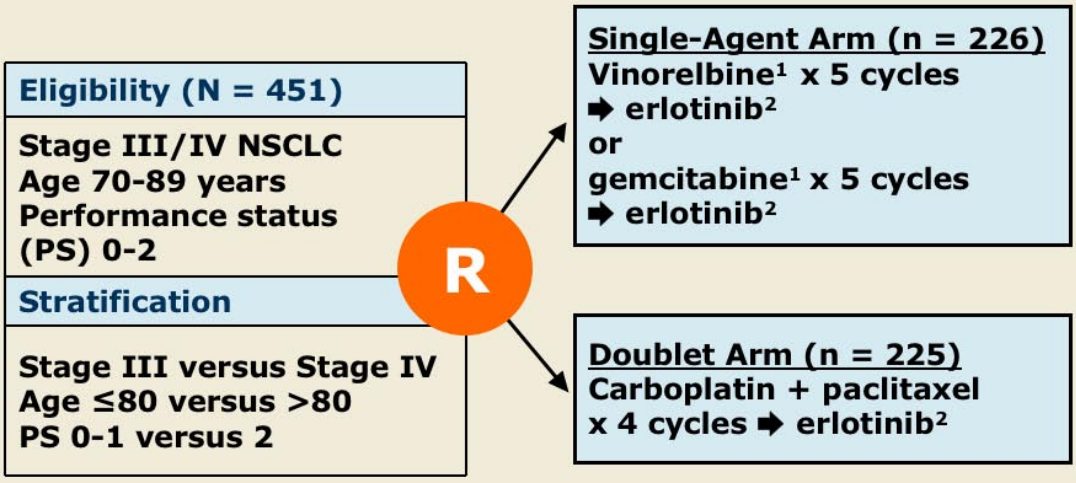
Trial Schema



[1] Choice of vinorelbine or gemcitabine decided by center at the beginning of the study
[2] Erlotinib given in cases of progressive disease or excessive toxicity

Quoix EA et al. *Proc ASCO* 2010;Abstract 2.

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Response Rate at Six Weeks (ITT)

	Single agent (n = 211)	Doublet (n = 210)	*p*-value
Partial response (PR)	10.90%	29.05%	$<10^{-5}$
Stable disease (SD)	45.50%	38.57%	0.18
Disease control rate (DCR) (PR + SD)	56.40%	67.62%	0.02
Progressive disease (PD)	21.80%	7.14%	$<10^{-4}$
Not reported	7.11%	9.53%	0.47
Withdrawal before first evaluation*	14.70%	15.70%	0.88

* Main causes: Deaths (20 in single-agent arm and 23 in doublet arm), reduced general condition (7 and 4, respectively), toxicity (0 and 4, respectively) and withdrawal of consent (6)

Quoix EA et al. *Proc ASCO* 2010;Abstract 2.

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Survival Data (ITT)

	Single agent (n = 226)	Doublet (n = 225)	*p*-value
Progression-free survival (PFS) Median (95% CI) 1-year PFS rate (95% CI)	 3.0 months (2.6-3.9) 2.3% (0.8-5.3)	 6.1 months (5.5-8.7) 15.4% (10.8-20.8)	$<10^{-6}$
Overall survival (OS) Median (95% CI) 1-year OS rate (95% CI)	 6.2 months (5.3-7.4) 26.9% (21-33.1)	 10.3 months (8.3-13.3) 45.1% (38.2-51.8)	0.00004

Quoix EA et al. *Proc ASCO* 2010;Abstract 2.

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Select Grade 3/4 Toxicities

	Gem (n = 149)	Vin (n = 61)	All single agent	Doublet (n = 208)	*p*-value
Neutropenia	4.70%	37.70%	14.30%	54.30%	$<10^{-5}$
Febrile neutropenia	0%	9.84%	2.90%	9.60%	0.004
Anemia	2.01%	9.84%	4.30%	7.70%	0.14
Thrombocytopenia	1.34%	0%	1.00%	6.30%	0.004
Neuropathy	0%	0%	0%	2.90%	0.015
Asthenia	6.04%	6.56%	6.20%	9.60%	0.19
Anorexia	1.34%	0%	1.00%	3.80%	0.061
Reduced general condition	0.67%	3.28%	1.50%	1.40%	1.0

Quoix EA et al. *Proc ASCO* 2010;Abstract 2.

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Conclusions

- First study entirely devoted to elderly patients showing the superiority of a carboplatin doublet over single-agent therapy in advanced NSCLC.
  - Median PFS: 6.1 mo vs 3.0 mo ($p < 10^{-6}$)
  - Median OS: 10.3 mo vs 6.2 mo ($p = 0.00004$)
  - 1-yr OS rate: 45% vs 27%
- Doublet had a beneficial effect on survival in most of the subgroups tested, even those with worse prognosis (data not shown).
- Doublet regimen had acceptable toxicity.
- New paradigm for elderly patients with advanced NSCLC: Monthly carboplatin plus weekly paclitaxel.

Quoix EA et al. *Proc ASCO* 2010;Abstract 2.

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Investigator comment on the results of IFCT 0501: A Phase III study of combination versus single-agent chemotherapy for elderly patients with advanced NSCLC

This plenary presentation focused on elderly patients who were 70 years or older with advanced NSCLC was notable and important. Whether these patients should receive single-agent or combination chemotherapy has been debatable because the results of previous studies have been mixed.

This was a large European study, which randomly assigned patients to weekly paclitaxel with carboplatin or single-agent therapy. Although we need better therapy than was utilized in either of these arms, the study clearly demonstrated superiority for the combination regimen. The combination was a little more toxic than the single agent, but overall the tolerability was good. I believe it's now clear that we should treat elderly patients without severe comorbidities as we treat younger patients. Many of us have believed for years that this was the appropriate way to treat older patients, and this study confirms it.

Interview with F Anthony Greco, MD, June 15, 2010

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Investigator comment on the results of IFCT 0501: A Phase III study of combination versus single-agent chemotherapy for elderly patients with advanced NSCLC

This study met its primary endpoint in that the doublet chemotherapy was superior to the singlet, with median progression-free survival doubling from 3 to 6.1 months and the median overall survival improving from 6.2 to 10.3 months. This is quite significant.

Of course the question is, at what cost? In terms of nonhematologic toxicity, slightly more neuropathy was associated with the combination — 2.9 percent Grade 3 or 4 neuropathy — and possibly a trend for more anorexia. For hematologic toxicity, there was a little more neutropenia — 54.3 percent versus 37.7 percent Grade 3 or 4 neutropenia — which did translate to slightly more febrile neutropenia, and there was also more thrombocytopenia. Toxic deaths were also slightly more common with the combination regimen.

Clearly the benefit of the doublet versus single-agent therapy is significant, and one should consider using a platinum-based doublet for elderly patients with advanced NSCLC. The bottom line is that this study should cause us to revisit the standard approach for elderly patients with good performance statuses.

Interview with Roy S Herbst, MD, PhD, June 23, 2010

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Investigator comment on the results of IFCT 0501: A Phase III study of combination versus single-agent chemotherapy for elderly patients with advanced NSCLC

This study for the elderly is near and dear to my heart because this has been an area of particular interest to me. I have done several retrospective analyses in patients 70 years of age or older and have consistently shown, at least in North America, that fit older patients fare as well or nearly as well as younger patients, but that mind-set is not universal. In Europe a single agent remains the standard for elderly patients with advanced NSCLC. In the NCCN and ASCO guidelines a single agent is certainly the preferred approach, although some allowance is made for combination therapy.

This study by Quoix and colleagues is paradigm shifting. They were able to accomplish what no other group has previously been able to do, which is to compare a platinum-based doublet to single-agent therapy, and they demonstrated convincingly and overwhelmingly that the doublet was superior in every imaginable way.

For myself, a platinum-based doublet, preferably carboplatin-based, is the standard, and I believe carboplatin and weekly paclitaxel will be the reference arm for future studies for the elderly.

Interview with Corey J Langer, MD, July 2, 2010

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