Impact of the ASCO 2007 Presentation of HOG Lun 01-24/ USO-023 on the Prescribing Plans of American Medical Oncologists for Patients with Stage IIIB Non-small Cell Lung Cancer

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Introduction: Nonoperative treatment of stage III non-small cell lung cancer has evolved over the past 30 years. The current approach in the Unites States most often includes concurrent chemoradiotherapy.

Methods: We have used live, case-based research events to document prescribing plans among American medical oncologists for first-line therapy in patients with N3 stage IIIB non-small cell lung cancer. Changes in prescribing plans documented before and after the 2007 American Society of Clinical Oncology (ASCO) presentation of a Hoosier Oncology Group trial testing the role of consolidation docetaxel chemotherapy in this setting are presented.

Results: Data from 2007 show a post-ASCO shift away from plans for docetaxel consolidation, increased use of concurrent chemoradiotherapy alone, and stable to increased plans for concurrent chemoradiation followed by additional cycles of the chemotherapy used during concurrent management (20%). Preliminary data from 2008 confirm the durability of these changes.

Conclusions: The findings of the Hoosier Oncology Group trial support a transition away from docetaxel consolidation. A trend in this direction among American medical oncologists is clear from our data. However, nearly 20% of oncologists studied in 2008 still plan to use docetaxel consolidation. Furthermore, a majority of those studied after ASCO 2007 continue to report plans to use more than two cycles of chemotherapy as part of their preferred treatment recommendation despite no level I evidence to support this approach.

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The most recent figures from the American Cancer Society suggest that we should expect 215,000 new cases of lung cancer in 2008. Approximately 85% of these new cases will have nonsmall cell histology and about one third will have regional (N2–N3) disease at the time of diagnosis.[1] Based on these figures, nearly 64,000 individual Americans should be identified with stage III non-small cell lung cancer (NSCLC) during this calendar year.

Nonoperative treatment of stage III NSCLC has evolved during the past 30 years from largely palliative radiation therapy, through sequential chemotherapy followed by radiation, to the current use of concurrent chemoradiotherapy.[2] In many cases, physicians have used two to four additional chemotherapy cycles as either induction or consolidation therapy with the expectation that the added chemotherapy would improve survival. In 2006, data from a Cancer and Leukemia Group B randomized phase III trial failed to demonstrate a survival advantage for the addition of two cycles of full-dose carboplatin-paclitaxel followed by definitive radiation and concurrent weekly paclitaxel-carboplatin compared with definitive radiation and concurrent weekly paclitaxel-carboplatin alone.[3] However, up until recently, phase II data reported by multiple investigators suggested that immediate concurrent chemoradiotherapy followed by consolidation chemotherapy produced excellent outcomes for nonoperative therapy in stage III patients. One such approach developed by Southwest Oncology Group (SWOG) investigators involved immediate concurrent etoposide-cisplatin and radiotherapy followed by three cycles of docetaxel.[4] Another approach using immediate concurrent carboplatin-paclitaxel radiation followed by two additional cycles of every 3-week paclitaxel-carboplatin was reported by Belani et al.[5] Data on 978 American medical oncologists studied by investigators at Network for Medical Communications and Research (NMCR) Analytics between 2005 and before the 2007 American Society of Clinical Oncology (ASCO) Annual Meeting

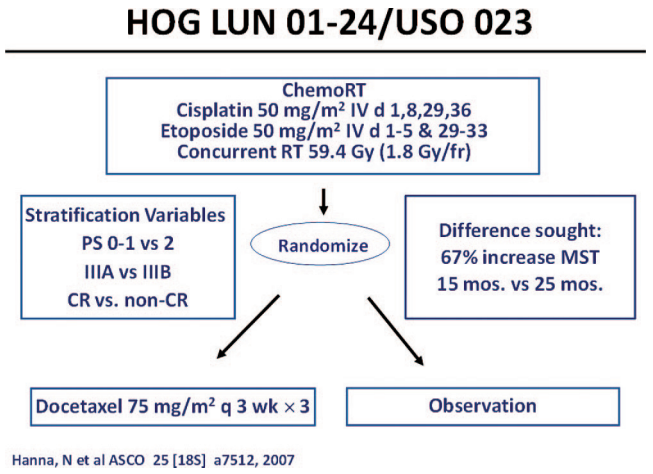

FIGURE 1. Schema for Hoosier Oncology Group (HOG) trial evaluating the role of docetaxel consolidation in patients with a new diagnosis of stage III non-small cell lung cancer (NSCLC).

showed that nearly 70% planned to use both concurrent chemoradiation and consolidation chemotherapy in this setting.[6]

At the 2007 ASCO meeting, investigators from the Hoosier Oncology Group[7] (HOG) reported that there was no survival advantage but significant toxicity from the addition of docetaxel consolidation to immediate radiation and concurrent etoposide-cisplatin (Figure 1). To assess the impact of these data, we documented the prescribing plans for nonoperative therapy for patients with N3 stage IIIB NSCLC among several hundred additional American medical oncologists. Here, we report those prescribing plans and discuss the impact of new phase III data on treatment strategies planned for patients with stage IIIB NSCLC.

METHODS

Since 2005, NMCR Analytics has studied prescribing plans of American medical oncologists for patients with stage III NSCLC using 14 individual live research events. Physicians participating in these research programs self-register through direct invitation or by means of the NMCR Analytics website. Attendees are reimbursed for research-related expenses including any travel costs incurred and specific out-of-pocket expenses. Attendees do not receive additional payments for their participation. Responses to research queries are treated confidentially, and no identifying information about individual participants is disclosed. Attendees may participate in only one lung cancer research event within a calendar year. Some of the prescribing plans recorded in the first two research events of 2008 may come from individuals also included in the prescribing plans tallied pre-ASCO 2007 or post-ASCO 2007.

Research programs are designed to mimic real-life clinical scenarios. The hypothetical case history is projected on the screen at the front of the meeting room and read aloud by the research event moderator. Treatment plan options (up to 10) are then offered, and physician selections are acquired anonymously and contemporaneously by keypad and electronic data capture before any discussion of relevant data supporting one or more of the possible prescribing plans offered. As soon as the participants have completed their selection (documented by real-time counter of responses), the results are tallied and projected in bar graph format.

Demographic information is collected from the participants at the beginning of each research session. The characteristics polled include practice venue (academic versus community and geographic region), number of partners, years from completion of training in oncology, number of new lung cancer patients seen each month, sex, and participation in a group purchasing organization. These features are entered into the wireless keypad by each attendee in response to specific questions. This information then gives each keypad a demographic character that can be used to analyze the respondent choices by subset while maintaining the anonymity of the individual participants.

To study current approaches in a patient with N3 stage IIIB NSCLC, we used a core case history and a "menu" of preset treatment plans (Figures 2, 3). Oncologists are very familiar with this approach. Case-based decision making is the standard format for tumor board or clinical case conference discussions of potential management options for individual patients. Although this format cannot encompass all possible treatment plans among the options offered (≤10), we include a broad range of relevant options including all relevant evidence-based strategies. An option of "other" is also included to avoid a forced choice. Not all attendees respond to every research question posed, but overall participation of more than 80% is achieved for each question.

A 66-year-old former smoker has a progressive cough. After an episode of hemoptysis (actually only a small amount of bloody sputum) he is seen in the ER where a chest x-ray and chest CT are done. There is a partially cavitated, medially located, RUL mass with enlarged hilar and N2 and N3 mediastinal nodes. A pulmonary medicine physician sees him and arranges an urgent bronchoscopy (TBB specimen positive for NSCLC NOS) and Wang needle aspiration of subcarinal nodes (also + for tumor). A PET scan is positive in these areas as well as the right hilum and the right and left paratracheal areas. A head MRI is negative for metastatic disease.

FIGURE 2. Case scenario for assessing prescribing plans of American medical oncologists. No changes were made in the case scenario during the entire period reported.

1. Immediate TRT followed by (f/by) CT
2. Induction CT f/byTRT
3. 2 cycles of induction CT f/by CT/TRT (same drugs as in induction)
4. CT/TRT (no induction or consolidation CT)
5. CT/TRT f/by 2 added cycles of the same CT used during radiation
6. CT/TRT f/by 3 doses of docetaxel
7. CT/TRT f/by 3 doses of docetaxel and then single agent erlotinib.
8. CT alone
9. Other

TRT = Thoracic radiotherapy; CT = Chemotherapy; CT/TRT = concurrent chemoradiotherapy

FIGURE 3. Prescribing plans offered as selection options for the research study participants. The option "other" is routinely included to avoid driving research participants to a "forced choice" selection.

RESULTS

Between March 2005 and May 2007, 978 medical oncologists participated in 12 live research events studying prescribing plans for different clinical settings in lung cancer. These individuals and those queried after the 2007 ASCO meeting were ~80% self-identified as "community based" and displayed a geographic spread reflective of the broad American Oncology workforce. Less than 25% were in solo practice, and a majority of all respondents were more than 10 years out from completion of their oncology training.

In the assessment of prescribing plans for the stage IIIB setting, a substantial majority of the 978 responding physicians planned to use concurrent chemoradiotherapy followed by additional chemotherapy (Figure 4). For 47% of physicians, the planned therapy was immediate chemoradiation followed by three doses of docetaxel consolidation. For 3%, the plan included the same chemoradiation followed by three doses of docetaxel consolidation and then additional maintenance therapy with an oral antiepidermal growth factor receptor tyrosine kinase inhibitor. An additional 17% of respondents favored the use of immediate chemoradiotherapy followed by two additional cycles of the same chemotherapy used during the concurrent phase of treatment.

In 2007, we studied an additional 427 physicians (preset participation goal >400) in five live research events held between March and September. Demographic characteristics of these research participants were similar to those of the earlier 987 physician cohort. These research events again used the same clinical scenario of stage IIIB disease and offered the same panel of therapy options. In Figure 5, the aggregate findings of the five research events of 2007 are shown, whereas in Figure 6, the data are broken down by pre-ASCO 2007 and post-ASCO 2007. The aggregate data do show a shift away from the use of immediate chemoradiotherapy followed by docetaxel consolidation (38%), a rise in the use of immediate concurrent chemoradiotherapy alone

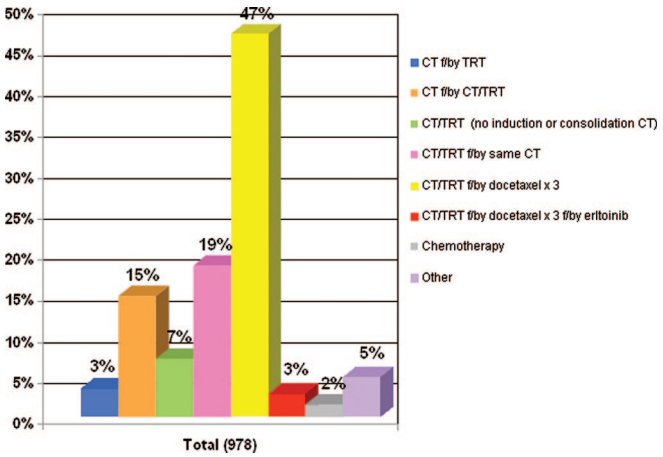

FIGURE 4. Prescribing plans for a patient with a new diagnosis of stage IIIB non-small cell lung cancer (NSCLC) assessed in 987 American medical oncologists who participated in Network for Medical Communications and Research (NMCR) live research events between March 2005 and May 2007.

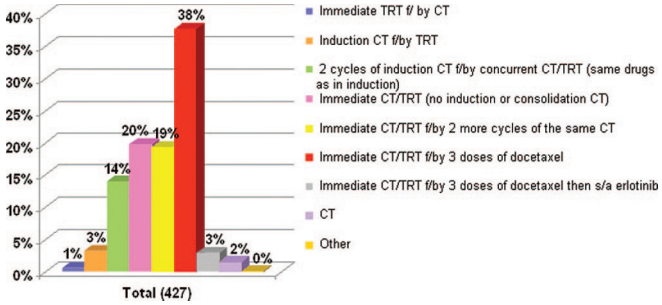

FIGURE 5. Prescribing plans for a patient with a new diagnosis of stage IIIB non-small cell lung cancer (NSCLC) assessed in 427 American medical oncologists who participated in Network for Medical Communications and Research (NMCR) live research events between March and September 2007.

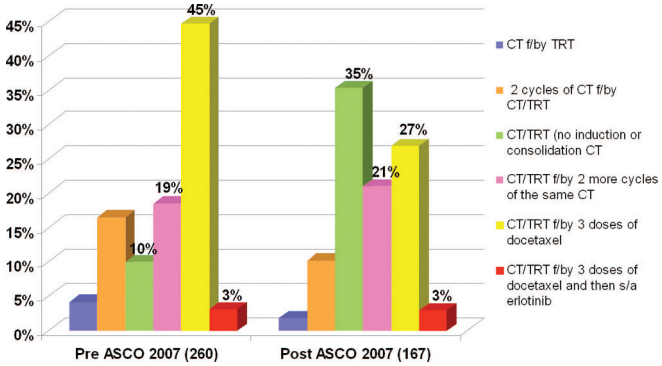

FIGURE 6. Prescribing plans for a patient with a new diagnosis of stage IIIB non-small cell lung cancer (NSCLC) assessed in 427 American medical oncologists who participated in Network for Medical Communications and Research (NMCR) live research events between March and September 2007. Prescribing plans shown for two time frames, before and after American Society of Clinical Oncology (ASCO) 2007. Choices of "radiation followed by chemotherapy," "chemotherapy alone," and "other," totaling 3% are not shown here.

(20%), and stable plans for use of immediate concurrent chemoradiation followed by two additional cycles of the same chemotherapy that was used in the concurrent phase of therapy (19%). However, the aggregate data (Figure 5) obscure a more dramatic time-dependent movement away from docetaxel consolidation (45% → 27%; χ^2 $p < 0.0002$) and toward immediate concurrent chemoradiotherapy without consolidation, the strategies compared directly in the HOG phase III trial.

In Figure 7, the 2007 data from each of the five research events are displayed individually. Presenting the data in this fashion further highlights the change driven by the 2007 ASCO presentation of the HOG trial data. Immediately after ASCO 2007, a shift in prescribing plans occurred. Its durability and further amplification are evident in the data from late September. After the acquisition of these data, we continued to monitor prescribing plans in 2008 (Table 1). In two research events in February and April 2008, plans for use of

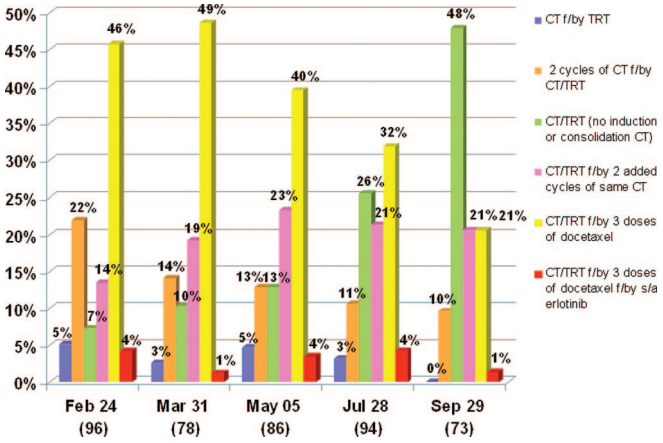

FIGURE 7. Prescribing plans for a patient with a new diagnosis of stage IIIB non-small cell lung cancer (NSCLC) assessed in 427 American medical oncologists who participated in Network for Medical Communications and Research (NMCR) live research events between March and September 2007. Prescribing plan data are shown for each specific research event with the inflection point coinciding with the Hoosier Oncology Group (HOG) data presentation at American Society of Clinical Oncology (ASCO) 2007.

TABLE 1. Prescribing Plan Data from Research Events Held in February 2008 and April 2008 Demonstrate the Persisting Shift Away from Use of Docetaxel Consolidation After ASCO 2007

Regimen	February 23, 2008, $n = 109$ (%)	April 05, 2008, $n = 61$ (%)
CT/TRT	1	5
CT-CT/TRT	8	10
CT/TRT (HOG)	39	44
CT/TRT-same CT (LAMP)	26	23
CT/TRT-doc (SWOG 9504)	19	18
CT/TRT-doc-erlotinib (0023)	3	0
CT alone	1	0
Other	1	0

CT/TRT, chemotherapy/thoracic radiotherapy; HOG, Hoosier Oncology Group; LAMP, locally advanced multi-modality protocol; SWOG, Southwest Oncology Group.

consolidation docetaxel have fallen to less than 20% of research respondents. The largest single group now plans to use immediate concurrent chemoradiotherapy without either induction or consolidation. However, the ambivalence of the treating oncology community is clear, with a majority of all respondents planning some treatment strategy that includes more than just two cycles (or equivalent) of chemotherapy during radiation as total therapy in the stage IIIB setting.

DISCUSSION

Individuals diagnosed with a contralateral-mediastinal, N3, stage IIIB NSCLC are seeking the best therapy option to provide them with the longest duration of quality life. They recognize that there may be some individual potential to achieve long-term disease control, although the best strategy for optimizing this goal is unclear. For fit individuals with a diagnosis of N3, stage IIIB NSCLC, the treatment recommendations of American medical oncologists almost always involve both chemotherapy and radiation. These two modalities are designed to both maximize control of the macroscopic locoregional disease and eradicate micrometastatic foci that are also highly likely to be present. Currently, phase III trial data from numerous sources suggest that use of concurrent chemoradiotherapy can increase overall survival when compared directly with the same therapies given sequentially. The survival advantage is modest however, and there are additional toxicities associated with concurrent rather than sequential management.[2]

The potential of chemotherapy to effectively eradicate micrometastases and improve survival when used in the adjuvant setting has been demonstrated among patients with many different types of solid tumors including NSCLC.[8] In almost all these settings (testis cancer being a notable solid tumor exception), the adjuvant chemotherapy prescription has included more than two cycles of chemotherapy. Thus, when approaching an individual with more disease (e.g., stage IIIB NSCLC) and the expectation that the burden of micrometastatic disease is likely to be at least as great if not greater than in the traditional adjuvant setting, investigators and treating physicians have tended to favor strategies using more than two cycles of chemotherapy as part of definitive management.[2] Yet, no randomized phase III data are available to endorse this approach in stage III NSCLC. However, as demonstrated here, before ASCO 2007 the use of more than two cycles of chemotherapy was the overwhelming plan of American medical oncologists treating patients with N3, stage IIIB disease. For nearly 70%, the additional chemotherapy was planned as consolidation and for most of those the consolidation involved use of single-agent docetaxel. This approach was supported by impressive multiinstitutional phase II data provided by investigators from the SWOG. In their phase II work (SWOG 9504),[4] the median survival achieved with immediate concurrent etoposide-cisplatin and thoracic radiation followed by three cycles of docetaxel consolidation was 26 months and the 3- and 5-year survival rates were 40% and 29%, respectively.[4] In a previous SWOG study in patients with stage III disease using the same initial chemoradiotherapy but followed by consolidation with two added cycles of etoposide and cisplatin, the median survival was 15 months and 3- and 5-year survival rates were 17%.[9] These phase II findings and informal comparison generated major enthusiasm for the SWOG 9504 approach. After lengthy discussions with representatives from the National Cancer Institute's Cancer Therapy Evaluation Program, the follow-up phase III trial proposed by SWOG investigators to confirm the benefit of consolidation docetaxel that was implied by their sequential phase II trials was not approved. Instead, an alternative design that presumed a benefit from consolidation docetaxel and tested the value of maintenance gefitinib (SWOG S0023) was moved forward.[10]

At ASCO 2007, findings from the HOG phase III (albeit modest in size) trial testing immediate concurrent

chemoradiotherapy as used by SWOG with or without docetaxel in patients with stage III NSCLC were presented by Hanna et al.[7] Although some of the patients included in this study had baseline characteristics, especially less optimal pulmonary function, that were different from the SWOG study participants, the core comparison of CT/TRT with or without consolidation addressed the critical question of whether the addition of consolidation chemotherapy would significantly improve the survival outcome in patients with stage III NSCLC. The data from the 2007 presentation were clear. In every relevant treatment-efficacy comparison there was no improvement, let alone no significant benefit, for the addition of docetaxel consolidation. At ASCO 2008, further follow-up of the HOG trial again showed no benefit from docetaxel consolidation.[11] However, the 2007 presentation did highlight the toxicity risks associated with docetaxel consolidation. These included a 24.7% rate of grade 3 or 4 neutropenia, a 10.9% rate of febrile neutropenia, an 8.2% rate of grade 3 pneumonitis, and a 5.5% treatment related death rate.

The findings of the HOG trial support a transition away from docetaxel consolidation,[12] and the trend in this direction among American medical oncologists is clear from our data. However, two surprising results of our research are evident. First and foremost, nearly 20% of those oncologists studied in 2008 are still planning a SWOG 9504 approach with docetaxel consolidation. This seems difficult to justify in light of the toxicity produced by this strategy and the failure of the phase III comparison to suggest any benefit. Whether the SWOG Lung committee will decide to retest a chemoradiotherapy followed by consolidation strategy remains to be seen. More globally, a majority of all the oncologists studied after ASCO 2007 continue to report plans to use more than two cycles of chemotherapy as part of their preferred treatment recommendation for fit patients with stage III NSCLC. For the largest single subgroup of those oncologists, the preferred recommendation now involves immediate induction chemoradiotherapy followed by two added cycles of the same chemotherapy in the consolidation setting. Although this decision is consistent with the model of adjuvant chemotherapy widely applied in patients with completely resected solid tumors, there are no phase III data in the lung cancer setting to support it, and the toxicity risks and economic costs associated with it are formidable. Currently, there are no plans among the American National Cancer Institute sponsored cooperative groups to retest the role of chemotherapy consolidation, e.g., immediate concurrent chemoradiation with or without two added cycles of the same chemotherapy as consolidation. Although such a trial would add to the evidence base in stage III disease, there are scant to no compelling phase II data that support such a resource-intensive undertaking.

The changing approach to definitive nonoperative management of patients with stage III NSCLC is clearly demonstrated by our research. We will continue to monitor prescribing plans proposed by American medical oncologists for patients with regionally advanced NSCLC. It is hoped that the trends away from docetaxel consolidation will continue. This is a critical setting in which patients with a new diagnosis of stage III NSCLC and their treating oncologists should come together to participate in well-designed clinical trials with the potential to generate new leads or definitive data concerning better approaches to achieve the jointly shared goal of a longer duration of quality life and an enhanced opportunity for long-term disease control.

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