CLINICAL VIGNETTE

A Case of Multiple Malignancies and Long Term Survival in a Non-Smoking Chinese Female with Stage III B Non Small Cell Lung Cancer

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Case Report

A 63-year-old non smoking Chinese female presented in June 2004 with cough and shortness of breathe. Examination revealed a right supraclavicular mass. Staging scans with PET/CT imaging demonstrated a 5.7 x 5/4 x 6.0 CM R suprahilar mass with 3 pretracheal nodes as well as a 1.8x 1.8 cm right supraclavicular mass. (T3, N3, stage IIIB) Percutaneous lung biopsy demonstrated a moderately differentiated adenocarcinoma. EGFR testing was positive for the mutation. The patient was treated with carboplatin and docetaxel for 6 cycles with concurrent radiation therapy (RT) at cycle 2-3. At the time of imaging 2 months after RT and on completion of carboplatin/docetaxel, the patient developed mild radiation pneumonitis and ipsilateral pleural effusion. PET showed near complete resolution (CR) but it was unclear if this represented RT pneumonitis or residual disease. The pt was treated successfully with steroids with resolution of symptoms. She was placed on erlotinib for 5 years and she remains disease free at year 9.

Over the course of follow up she has developed three other malignancies: papillary thyroid cancer treated with thyroidectomy and I 131 therapy; Low grade appendiceal carcinoma treated with surgical resection; and follicular low grade non Hodgkin lymphoma in the left axilla treated with excisional biopsy.

Discussion

Stage III B non-small cell carcinoma of the lung is felt to be unresectable in most settings with radiation and chemotherapy in combination being the mainstay of treatment. Concurrent chemotherapy with radiation has been shown to be superior to sequential therapy. Most studies show statistically improved median survival with combined modality therapy (chemotherapy and radiation) with 5 yr survival ranging from 5-15%[1-4].

The best chemotherapeutic regimen has not been determined given the rapid evolution of newer agents in lung cancer, however, several well studied regimens include cisplatin/etoposide, carbo/ paclitaxel and cisplatin/pemetrexed. In the Southwest Oncology Group trial using cisplatin/etoposide with concurrent RT, three and 5 yr survival was 17 and 15%, respectively[5]. Several studies have extended chemotherapy past RT, with varying results. A similar regimen given to this patient was reported by Belani, Choy, Bonomi et al (paclitaxel instead of docetaxel) which included a consolidation phase of continued chemotherapy with paclitaxel after RT with median survival reported at 16.3 months[6,7].

The case raises several issues including assessment of residual disease, and the benefit and length of therapy for maintenance or consolidation therapies. CT scans have been the mainstay of staging and follow up for locally advanced and metastatic disease. PET scanning recently has been added to the options for lung cancer staging. Integrated PET/CT has good negative predictive value but poor positive predictive value especially when used to determine nodal disease[8]. In this case initial PET/CT scanning as well as palpable supraclavicular disease staged the disease definitively at IIIB. In other cases, with lower tumor burden, a PET positive hilar or mediastinal node would require definitive biopsy to determine if the imaging findings reflect malignancy.

PET/CT scanning for follow up after definitive chemotherapy and RT may also demonstrate false positive results. For that reason, NCCN guidelines do not recommend routine follow up with PETCT imaging because “restaging after induction therapy is difficult to interpret”[9]. Radiation pneumonitis is a well-know cause of false positive PET/CT scans. The

acute phase of radiation is the first 1- 8 weeks and our patient may have been scanned earlier than optimal[10]. Ideally, chronic fibrotic changes in the radiation field on the CT portion of the scan would allow for correct interpretation of the PET/CT scan[10]. These findings were not evident for this patient. It was concluded that the patient had an excellent but possibly not complete response to chemotherapy and RT.

Given the excellent but unclear response to chemotherapy and RT and 2 additional cycles of chemo, erlotinib was started. Erlotinib was initiated for both therapeutic as well as maintenance purposes. At that time, maintenance strategies were being evaluated in investigational trials. Now, maintenance therapies with single agents have demonstrated improvement in progression free survival in several studies[11,12]. The most commonly used agents are pemetrexed, gemcitabine, docetaxel and epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKI). Data from the SATURN trial, which randomized patients with advanced lung cancer to maintenance erlotinib or placebo, demonstrated that erlotinib improves progression free survival, especially in EGFR mutant tumors[13].

This patient was treated for 5 years with erlotinib. Traditionally, patients with advanced disease are kept on a tolerable treatment regimen indefinitely until disease progression. The patient's PET/CT scan normalized at year 2. After review of serial scans, it was felt that the patient did not have residual disease at the time of initiation of maintenance therapy. Given that she did not have proven distant metastatic disease or active local regional disease after definitive chemotherapy with RT, combined with toxicity from erlotinib with significant skin rash and diarrhea for most of the 5 yrs of therapy, the erlotinib was stopped. She remains disease free at 9 year.

Over the course of the last 5 years, this patient developed papillary thyroid cancer, low grade appendiceal carcinoma and follicular low-grade non Hodgkin lymphoma all treated with curative intent with likelihood of recurrence. She has no active subsequent cancers and there is no evidence linking her original carcinoma or its treatment with these subsequent cancers. The nature of these malignancies suggests that they occurred without a genetic predisposition.

In conclusion, this case demonstrates that long-term survival is feasible in a small subset of patients with Stage III B non-small cell lung cancer, even though such patients are not candidates for surgical resection. The newer systemic agents, combined with radiation therapy and maintenance therapies, have improved progression free survival in advanced non-small cell lung cancer, while offering long term survival in a small subset of these patients.

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REFERENCES

1. **Dillman RO, Herndon J, Seagren SL, Eaton WL Jr, Green MR**. Improved survival in stage III non-small-cell lung cancer: seven-year follow-up of cancer and leukemia group B (CALGB) 8433 trial. *J Natl Cancer Inst*. 1996 Sep 4;88(17):1210-5. PubMed PMID: 8780630.
2. **Sause WT, Scott C, Taylor S, Johnson D, Livingston R, Komaki R, Emami B, Curran WJ, Byhardt RW, Turrisi AT, et al**. Radiation Therapy Oncology Group (RTOG) 88-08 and Eastern Cooperative Oncology Group (ECOG) 4588: preliminary results of a phase III trial in regionally advanced, unresectable non-small-cell lung cancer. *J Natl Cancer Inst.* 1995 Feb 1;87(3):198-205. PubMed PMID: 7707407.
3. **Sause W, Kolesar P, Taylor S IV, Johnson D, Livingston R, Komaki R, Emami B, Curran W Jr, Byhardt R, Dar AR, Turrisi A 3rd**. Final results of phase III trial in regionally advanced unresectable non-small cell lung cancer: Radiation Therapy Oncology Group, Eastern Cooperative Oncology Group, and Southwest Oncology Group. *Chest*. 2000 Feb;117(2):358-64. PubMed PMID: 10669675.
4. **Okawara G, Mackay JA, Evans WK, Ung YC**; Lung Cancer Disease Site Group of Cancer Care Ontario's Program in Evidence-based Care. Management of unresected stage III non-small cell lung cancer: a systematic review. *J Thorac Oncol*. 2006 May;1(4):377-93. Review. PubMed PMID: 17409887.
5. **Albain KS, Crowley JJ, Turrisi AT 3rd, Gandara DR, Farrar WB, Clark JI, Beasley KR, Livingston RB**. Concurrent cisplatin, etoposide, and chest radiotherapy in pathologic stage IIIB non-small-cell lung cancer: a Southwest Oncology Group phase II study, SWOG 9019. *J Clin Oncol*. 2002 Aug 15;20(16):3454-60. PubMed PMID: 12177106.
6. **Belani CP, Choy H, Bonomi P, Scott C, Travis P, Haluschak J, Curran WJ Jr.** Combined chemoradiotherapy regimens of paclitaxel and carboplatin for locally advanced non-small-cell lung cancer: a randomized phase II locally advanced multi-modality protocol. J Clin Oncol. 2005 Sep 1;23(25):5883-91. Epub 2005 Aug 8. Erratum in: *J Clin Oncol*. 2006 Apr 20;24(12):1966. PubMed PMID: 16087941.
7. **Gandara DR, Chansky K, Albain KS, Leigh BR, Gaspar LE, Lara PN Jr, Burris H, Gumerlock P, Kuebler JP, Bearden JD 3rd, Crowley J, Livingston R**; Southwest Oncology Group. Consolidation docetaxel after concurrent

chemoradiotherapy in stage IIIB non-small-cell lung cancer: phase II Southwest Oncology Group Study S9504. *J Clin Oncol*. 2003 May 15;21(10):2004-10. PubMed PMID: 12743155.

8. **Gámez C, Rosell R, Fernández A, Andía E, Arnáiz MD, Cardenal F, Lorenzo C**. PET/CT fusion scan in lung cancer: current recommendations and innovations. *J Thorac Oncol*. 2006 Jan;1(1):74-7. Review. PubMed PMID: 17409831.
9. NCCN Guidelines, 2013.
10. **Long NM, Smith CS**. Causes and imaging features of false positives and false negatives on F-PET/CT in oncologic imaging. *Insights Imaging*. 2011 Dec;2(6):679-698. Epub 2011 Sep 9. PubMed PMID: 22347986; PubMed Central PMCID: PMC3259390.
11. **Cappuzzo F, Ciuleanu T, Stelmakh L, Cicenas S, Szczésna A, Juhász E, Esteban E, Molinier O, Brugger W, Melezínek I, Klingelschmitt G, Klughammer B, Giaccone G**; SATURN investigators. Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomised, placebo-controlled phase 3 study. *Lancet Oncol*. 2010 Jun;11(6):521-9. doi: 10.1016/S1470-2045(10)70112-1. Epub 2010 May 20. PubMed PMID: 20493771.
12. **Ciuleanu T, Brodowicz T, Zielinski C, Kim JH, Krzakowski M, Laack E, Wu YL, Bover I, Begbie S, Tzekova V, Cucevic B, Pereira JR, Yang SH, Madhavan J, Sugarman KP, Peterson P, John WJ, Krejcy K, Belani CP**. Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomised, double-blind, phase 3 study. *Lancet*. 2009 Oct 24;374(9699):1432-40. doi: 10.1016/S0140-6736(09)61497-5. Epub 2009 Sep 18. PubMed PMID: 19767093.
13. **Brugger W, Triller N, Blasinska-Morawiec M, Curescu S, Sakalauskas R, Manikhas GM, Mazieres J, Whittom R, Ward C, Mayne K, Trunzer K, Cappuzzo F**. Prospective molecular marker analyses of EGFR and KRAS from a randomized, placebo-controlled study of erlotinib maintenance therap in advanced non-small-cell lung cancer. *J Clin Oncol*. 2011 Nov 1;29(31):4113-20. doi: 10.1200/JCO.2010.31.8162. Epub 2011 Oct 3. Erratum in: *J Clin Oncol*. 2011 Dec 10;29(35):4725. PubMed PMID: 21969500.

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