



Introduction

Lung cancer is the leading cause of cancer-related mortality in Canada and USA [1]. The American Cancer Society has estimated that in 2011 over 200 000 patients will be newly diagnosed with lung cancer, more than 15 000 patients will die of this disease. Non-small cell lung cancer (NSCLC) accounts for approximately 87% of lung cancers [2,3].

For last decades systemic chemotherapies especially platinum based doublets, have been used to treat NSCLC, but outcome improvements have reached a plateau [4,5]. The median survival when platinum-based doublets are administered for advanced NSCLC has improved from 4 to 5 months if untreated to 8–10 months, but this treatment causes significant toxicities, which limit the number of cycles to be administered [6].

Current treatment algorithms for the treatment of NSCLC recommend both histologic and molecular diagnostics [7]. Recent advances in our understanding of malignant cell signaling pathways, their interconnections, importance of different receptors, biomarkers, and the interplay between various oncogenes have led to the development of targeted treatments which are improving efficacy and also the treatment safety. These treatments are aimed at specific, especially genetic changes of the malignant cells. Different NSCLC subtypes are associated with potentially targetable biomarker such as epidermal growth factor receptor (EGFR) mutations [8–12] – KRAS mutations [13] – echinoderm microtubule – associated protein like 4 (EML4), anaplastic lymphoma kinase (ALK) or fusion genes (EML4–ALK) [14,15] and c-MET over expression or amplification [16–19].

Our hope is to apply the knowledge of the treatments with targeted agents acquired in advanced stages of NSCLC to the earlier stages of NSCLC, too, thus being able to increase the NSCLC cure-rate. Combining different targeted agents or sequencing

them properly will be very important in the new era of targeted individualized therapy.

In this publication, we will describe the importance of a team work from obtaining the tumor tissue, pathological diagnosis, molecular analysis, staging of the disease, the different treatments all the way to supportive care. You will learn about the different interventional procedures in order to obtain a satisfactory tumor specimen for analysis by pathologist and molecular biologists, to radiation and medical oncologist's treatments and ending with supportive care of patients. By this, we hope to give a complete review and guidelines for present and future approach to NSCLC patients.

References

- [1] Canadian Cancer Society. Canadian cancer statistics 2010. Statistics Canada, Public Health Agency of Canada, <http://www.cancer.ca> Accessed September 14, 2010.
- [2] National Cancer Institute. Non-small cell lung cancer treatment PDQ®: health professional version. <http://www.cancer.gov/cancertopics/pdq/treatment/non-small-cell-lung/healthprofessional> Accessed September 12, 2010.
- [3] Pisters KM, Evans WK, Azzoli CG, et al. Cancer Care Ontario and American Society of Clinical Oncology adjuvant chemotherapy and adjuvant radiation therapy for stages I–IIIA resectable non small-cell lung cancer guideline. *J Clin Oncol* 2007;25:5506–18.
- [4] Cagle PT, Allen TC, Dacic S, et al. Revolution in lung cancer: new challenges for the surgical pathologist. *Arch Pathol Lab Med* 2011;135:110–6.
- [5] Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N Engl J Med* 2002;346:92–8.
- [6] Cagle PT, Dacic S. Lung cancer and the future of pathology. *Arch Pathol Lab Med* 2011;135:293–5.
- [7] Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naïve patients with

- advanced-stage non-small-cell lung cancer. *J Clin Oncol* 2008;26:3543–51.
- [8] Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med* 2004;350:2129–39.
- [9] Paez JG, Janne PA, Lee JC, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science* 2004;304:1497–500.
- [10] Pao W, Miller V, Zakowski M, et al. EGF receptor gene mutations are common in lung cancers from “never smokers” and are associated with sensitivity of tumors to gefitinib and erlotinib. *Proc Natl Acad Sci U S A* 2004;101:13306–11.
- [11] Li AR, Chitale D, Riely GJ, et al. EGFR mutations in lung adenocarcinomas: clinical testing experience and relationship to EGFR gene copy number and immunohistochemical expression. *J Mol Diagn* 2008;10:242–8.
- [12] Uramoto H, Mitsudomi T. Which biomarker predicts benefit from EGFR-TKI treatment for patients with lung cancer? *Breast Cancer* 2007;96:857–63.
- [13] Sartori G, Cavazza A, Sgambato A, et al. EGFR and K-ras mutations along the spectrum of pulmonary epithelial tumors of the lung and elaboration of a combined clinicopathologic and molecular scoring system to predict clinical responsiveness to EGFR inhibitors. *Am J Clin Pathol* 2009;131:478–89.
- [14] Soda M, Choi YL, Enomoto M, et al. Identification of the transforming LML4-ALK fusion gene in non-small-cell lung cancer. *Nature* 2007;448(7153):561–6.
- [15] Wong DW, Leung EL, So KK, et al. The EML4-ALK fusion gene is involved in various histologic types of lung cancers from nonsmokers with wild-type EGFR and KRAS. *Cancer* 2009;115(8):1723–33.
- [16] Ma PC, Tretiakova MS, MacKinnon AC, et al. Expression and mutational analysis of MET in human solid cancers. *Genes Chromosomes Cancer* 2008;47:1025–37.
- [17] Okuda K, Sasaki H, Yukiue H, et al. Met gene copy number predicts the prognosis for completely resected non-small cell lung cancer. *Cancer Sci* 2008;99:2280–5.
- [18] Lutterbach B, Zeng Q, Davis LJ, et al. Lung cancer cell lines, harboring MET gene amplification are dependent on Met for growth and survival. *Cancer Res* 2007;67:2081–8.
- [19] Engelman JA, Zejnullahu K, Mitsudomi T, et al. MET amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling. *Science* 2007;316:1039–43.

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