Editorial

Induction Chemoimmunotherapy

Yasunori Sohara, MD

The number of deaths due to lung cancer in Japan was 52,177 (42 per 100,000) in 1999. This is approximately 2.5 times the number of 20 years ago and indicates that death to lung cancer has been increasing dramatically.

Treatments, including surgical therapy, radiotherapy, and chemotherapy, have been used to counter the rapid increases in lung cancer. The most efficacious treatment for non small-cell lung cancer (NSCLC) remains surgical therapy. However, 5-year survival rates (5Y-SR) from localized lung cancer without lymph node metastasis after surgical therapy alone of 70%, and 50% to 15% when metastases involve lymph nodes, is unsatisfactory.[1)] Systemic micrometastasis is the most important aggravating factor in the postoperative survival rate from NSCLC.[2)] Various combined therapies have been used to improve postoperative survival rates. Among these, postoperative radiotherapy has had little effect,[3)] and postoperative chemotherapy also has shown no obvious efficacy.[4-6)]

Induction chemotherapy (IC) has attracted attention recently. It was originally used to elevate inoperable lung cancer to an operable stage; however, it is now believed to be effective for both controlling systemic micrometastasis and diminishing primary tumors.[7)] IC was first attempted on advanced stage III lung cancer. The Sloan-Kettering group, which had the most cases (136 cases) in the study, reported that IC was not effective because the complete pathological response rate was as low as 14% and the postoperative death rate was unexpectedly as high as 5%.[8)] However, the Barcelona and Houston research groups reported that the 5Y-SR in IC patients was 21-25%, which was definitely better than that (3%) in non-IC patients.[9,10)] Other researchers found that more studies were necessary to confirm the efficacy of IC on stage III lung cancer.[11)]

We first performed postoperative chemotherapy when surgical therapy alone was not effective on stage III lung cancer, but we did not achieve the expected results that were reported from other institutions. We initiated IC using cis-diamino dichloreplatinum (CDDP) in 1995, after we began to see patients with unexpectedly high survival rates after IC for down staging. In the non-IC group, 5Y-SR were 45% and 35% for stages II and III, respectively; however, IC significantly improved the rates to 67% and 45%, respectively. We also applied IC to stage I lung cancers in 2001 based on the excellent results we obtained in stage II and III lung cancers; however, no conclusions have been obtained yet. IC has been also investigated in stage I and II lung cancers by diverse research groups in western countries.[12)]

Why is IC effective, whereas postoperative chemotherapy is not? After surgery, the immune system is suppressed by stress, resulting in augmentation of systemic micrometastasis.[13)] Postoperative chemotherapy decreases the endostatin release from primary tumors, which blocks suppression of vascular endothelial growth factor (VEGF) and results in augmentation of systemic micrometastasis.[14,15)] In other words, factors restraining micrometastasis are removed after surgery. To avoid this, it is necessary to eliminate as many systemic micrometastatic lesions as possible before surgery. We believe that IC is the most suitable method for this purpose.

I hypothesized that combining immunotherapy with IC in some form could block postoperative immune suppression. We conducted a study to compare the effects of single chemotherapy with CDDP, single immunotherapy with OK-432, chemotherapy after immunotherapy (CDDP after OK-432), and immunotherapy after chemotherapy (OK-432 after CDDP) in rats with lung cancer. The highest survival rate was observed in the group treated with OK-432 after CDDP, and the single immunotherapy group showed the worst result. In the group receiving OK-432 after CDDP, monocytes in peripheral blood increased; and many monocyte-type cells infiltrated the tumor, an effect which was not observed in the other groups. We believe that these results clearly show the reasons for failure in diverse, single immunotherapies.

From Department of Thoracic Surgery, Jichi Medical School, Tochigi, Japan

Address reprint requests to Yasunori Sohara, MD: Department of Thoracic Surgery, Jichi Medical School, Minamikawachi-machi, Tochigi 329-0498, Japan.

Intravascular antitumor lymphocytes need to contact tumor cells directly to establish antitumor immunity.[16,17] In single immunotherapy, intravascular antitumor lymphocytes are trapped inside tumor microvessel walls and do not contact tumor cells directly. However, chemotherapy prior to immunotherapy may break down tumor microvessel walls and allow antitumor lymphocytes to contact tumor cells. This theory may explain why chemotherapy after immunotherapy showed little effect. From these results, we believe that immunotherapy after chemotherapy (induction chemoimmunotherapy) not only blocks postoperative immune suppression but also augments antitumor immunity.[18,19] Clinical studies using this technique are continuing.

I hope that many other researchers and clinicians will concentrate on basic research and the clinical application of induction chemoimmunotherapy in the future, because it may be a highly effective treatment against lung cancer.

References

1. Mountain CF. Revision in the international system for staging lung cancer. *Chest* 1997; **111**: 1710–7.
2. Passlick B. Micrometastasis in non-small cell lung cancer (NSCLC). *Lung Cancer* 2001; **34**: S25–29.
3. Dautzenberg B, Arriagada R, Chammard AB, et al. A controlled study of postoperative radiotherapy for patients with completely resected nonsmall cell lung carcinoma. *Cancer* 1999; **86**: 265–73.
4. Niiranen A, Niitamo-Korhonen S, Kouri M, et al. Adjuvant chemotherapy after radical surgery for non-small-call lung cancer: a randomized study. *J Clin Oncol* 1992; **10**: 1927–32.
5. Feld R, Rubinstein L, Thomas PA. Adjuvant chemotherapy with cyclophosphamide, doxorubicin, and cisplatin in patients with completely resected stage I non-small-cell lung cancer. *J Natl Cancer Inst* 1993; **85**: 299–306.
6. Non-small Cell Lung Cancer Collaborative Group. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. *BMJ* 1995; **311**: 899–909.
7. Zandwijk NV. Neoadjuvant strategies for non-small cell lung cancer. *Lung Cancer* 2001; **34**: S145–150.
8. Martini N, Kris MG, Flehinger BJ, et al. Preoperative chemotherapy for stage IIIa (N2) lung cancer: the Sloan-Kettering experience with 136 patients. *Ann Thorac Surg* 1993; **55**: 1365–73.
9. Rosell R, Gomez-Codina J, Camps C, et al. Preresectional chemotherapy in stage IIIA non-small-cell lung cancer: a 7-year assessment of a randomized controlled trial. *Lung Cancer* 1999; **26**: 7–14.
10. Roth JA, Atkinson EN, Fossella F, et al. Long-term follow-up of patients enrolled in a randomized trial comparing perioperative chemotherapy and surgery with surgery alone in resectable stage IIIA non-small-cell lung cancer. *Lung Cancer* 1998; **21**: 1–6.
11. Eberhardt W, Bildat S, Korfee S, et al. Preoperative treatment strategies in stage III non-small cell lung cancer. *Lung Cancer* 2001; **33** (Suppl 1): S51–59.
12. Pister KMW, Ginsberg RJ, Giroux DJ, et al. Induction chemotherapy before surgery for early-stage lung cancer: a novel approach. *J Thorac Cardiovasc Surg* 2000; **119**: 429–39.
13. Sietses C, Beelen RH, Meijer S, et al. Immunological consequences of laparoscopic surgery, speculations on the cause and clinical implications. *Arch Surg* 1999; **384**: 250–8.
14. Yamaguchi N, Anand-Apte B, Lee M, et al. Endostatin inhibits VEGF-induced endothelial cell migration and tumor growth independently of zinc binding. *EMBO J* 1999; **18**: 4414–23.
15. Suzuki M, Iizasa T, Ko E, et al. Serum endostatin correlates with progression and prognosis of non-small cell lung cancer. *Lung Cancer* 2002; **35**: 29–34.
16. Basse P, Nannmark U, Johansson BR, et al. Establishment of cell-to-cell contact by adoptively transferred adherent lymphokine-activated killer cells with metastatic murine melanoma cells. *J Natl Cancer Inst* 1991; **83**: 944–950.
17. Nannmark U, Basse P, Johansson BR, et al. Morphological studies of effector cell-microvessel interactions in adoptive immunotherapy in tumor-bearing animals. *Nat Immun* 1996-97; **15**: 78–86.
18. Sohara Y, Murayama F, Endo S, et al. Vital microscopy for anti-tumor lymphocyte action in lung metastasis of SATO lung cancer. *Microcirculation annual* 1996; **12**: 197–8.
19. Sohara Y, Murayama F, Endo S, et al. NKT cells induced by chemo-immunotherapy suppress tumor growth - studies by vital observation of tumor microcirculation and lymphocyte analysis of peripheral blood. *Microcirculation annual* 1997; **13**: 17–8.