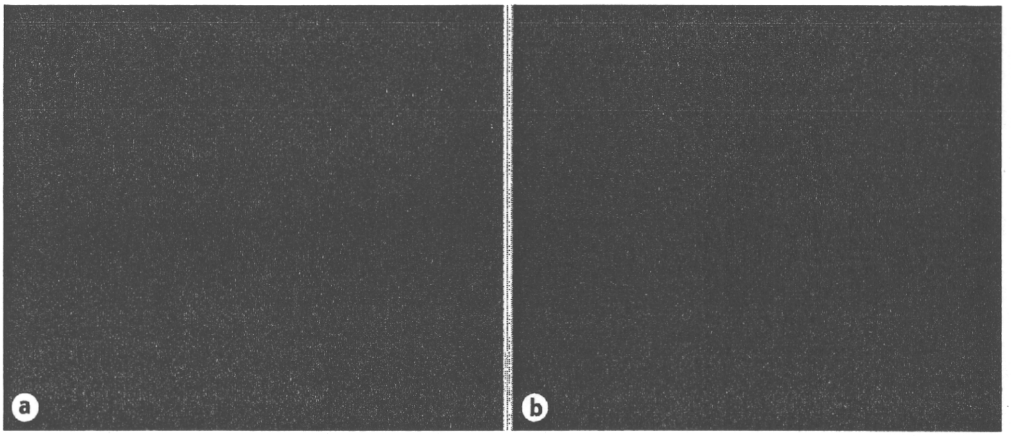

Fig. 3. NSCLC of the left lower lobe. T2/N1 tumor. FDG-PET-CT scan. **a** Before SBRT. **b** 12 months after SBRT with 5 × 7.0 Gy (calculated on the 60% isodose). Local lung fibrosis. Complete remission. SUV in PET scan <2. Courtesy of Institute of Nuclear Medicine, MRI, Munich.

overall survival rates were 93, 83 and 83%, respectively. In stage IB cancer, the local relapse-free survival rates were 100%. The disease-free survival after 1, 3 and 5 years were 92, 71 and 71%, respectively, and the overall survival rates were 82, 72 and 72%, respectively [39]. Onishi et al. [15] recently reported the results for 13 institutions in Japan, which summarized 245 patients: 155 with stage IA lung cancer and 90 with stage IB lung cancer. There were 87 operable and 158 inoperable patients, and their results showed that the intercurrent death rate was especially high in the inoperable patient group. Moreover, the 5-year survival rates of operable patients irradiated with more than BED = 100 Gy was 70.8% for the whole group, with 72.3% for stage IA and 65.9% for stage IB, and their clinical results were as good as those for surgery [15] (table 3).

These survival rates should be compared with the results of surgery; however, the results of SBRT may differ depending on how many patients of each groups are operable and inoperable, and how many of them have central and peripheral tumors. Additionally, the clinical staging is still less precise than the intraoperative one, mainly due to the detection of subclinical tumor spread around the primary and the higher detection rate of subclinical lymph node metastases by resection of N1 and N2 sites.

Side Effects

The great concern of pulmonary toxicity with this SBRT treatment was relieved by the very low rates of complications in early studies. Compared to conventional

radiotherapy, lung toxicity occurs relatively late after SBRT (e.g. 9–12 months or more). The most serious toxicity after SBRT for lung tumors is predominantly related to the bronchi and bronchioles located in the vicinity of the treated tumor. Frequently, dramatic imaging changes can be seen on CT scans consisting of in-field and downstream consolidation and fibrosis. Nevertheless, symptomatic radiation pneumonitis which consists of inflammation and fluid extravasation within the terminal bronchioles and alveoli is seen less frequently after SBRT than with conventional radiotherapy. Drop in oxygen exchange parameters, including diffusing capacity and arterial oxygen tension can be seen soon after treatment, but are scarce. Most pulmonary complications are less than NCI-CTC version 2.0 grade 2 (table 4).

The effects of a hypofractionated dose on the main bronchus, pulmonary artery, heart and esophagus have not been followed up for a sufficiently long time. However, a few serious complications have recently been reported by several institutions in Japan [72]. These complications include grade 5 pulmonary complications, radiation pneumonitis, hemoptysis and radiation esophagitis. Lethal pulmonary bleeding and esophageal ulcer have been previously reported by several authors. Timmerman [43] recently reported a series of complications with SBRT. Most cases of grade 5 radiation pneumonitis were accompanied by interstitial pneumonitis. Cases of interstitial pneumonitis should be carefully considered. Thoracocutaneous fistula was reported in a patient with previous tuberculosis history. Acute cholecystis was reported in a patient with gallstones who had been pressed with an abdominal press board at the time of SBRT. Finally, it is not uncommon for patients to experience chest wall pain months after SBRT, especially if treating tumors adjacent to the pleura, as a sign of intercostal neuralgia. Some, but not all, of these patients will have pleural effusions associated with chest wall pain. The problem seems to be mostly self-limited and conservative management with over-the-counter analgesics or anti-inflammatory medicines is typically effective. Some of those patients later develop rib fractures, which should be strongly separated from local tumor progression, either by FDG-PET scan or biopsy. When the esophagus, trachea or main bronchus are near the target, there is a higher risk of early dysphagia, severe cough, and late strictures [43, 73]. Therefore, central hilar tumors adjacent to mediastinal organs should be carefully considered for SBRT, or only treated with lower single fraction doses [32, 74] (table 4).

Comparison of SBRT with Surgical Data

Less than 25% of all patients diagnosed with lung cancer will present with early stage disease (less than 10% in stage I). These patients have the greatest hope for cure following standard procedure of resection. Survival varies, with reports on

5-year overall survival of 36–84% for pathologically proven stage IA and IB diseases [5]. Mean values on overall survival at 5 years of 67% for postoperative pathological stage IA and of 57% in stage IB are reported, with a difference of 8–38% between stage IA and IB. The results decrease to 61 and 37% for preoperative clinically defined stage IA and IB, respectively [4]. Mean 3-year overall survival rates of about 70% in stage IA and of less than 50% for stage IB are published for surgical treatment. These figures are comparable to data after SBRT alone.

Unfortunately, data sets on overall survival with a longer follow-up after initial staging with FDG-PET-CT are still limited. This makes a direct comparison of recent data of SBRT with results after curative resection difficult [56]. Considering disease-specific survival data one has to be aware of the fact that these are even more scarce than results concerning overall survival. Onishi et al. [15] were able to demonstrate in a large multicenter trial that overall survival after SBRT is comparatively better when patients are operable but refuse resection. In this subgroup of patients 3-year survival was significantly improved to 88% when a biological effective dose of more than 100 Gy was applied. These results are even better than those usually achieved by surgical procedures.

We know from surgical data that even in patients with good general condition a difference of up to 20% between overall and disease-specific survival can be detected following resection, with a disease-specific survival of 72% for stage IA and of 32% for stage IB at 5 years [6]. For all stage I patients the disease-specific survival at 3 years was reported to be about 64%, which is even worse in comparison to data of SBRT [15, 32].

Comparable to surgical data, cancer relapse following SBRT is usually distant. Less than 10% of the patients die due to local recurrence, but more than 20% from distant metastases, predominately in brain and lung. This indicates that NSCLC is in part a systemic disease even in clinical stage I cancer patients. The use of additional systemic chemotherapy might be of benefit for selected patients after hSRT, such as those younger than 75 years. After resection the positive effect on survival has already been demonstrated in randomized clinical trials [3].

Follow-Up Recommendations

Follow-up of patients has a crucial aspect in quality assurance of the treatment. It should allow for assessment of efficacy of treatment in terms of local tumor control, patient condition in terms of clinically relevant side effects and patient selection in terms of survival and/or progression of disease.

Clinical anamnesis and focal physical examination are the basic diagnostic methods. For assessment of local tumor control and clinically not obvious side effects laboratory tests (differential blood account, tumor marker), CT, MRI, FDG-

PET and/or spirometry can be performed. The first examination is usually 6 weeks after irradiation followed by further examinations every 3–6 months. The results and especially the acquired images should be sent to and co-evaluated by the treating physician, because assessment of changes such as distinguishing scar tissue and inflammation from tumor (recurrence) might be difficult and requires a certain amount of experience [57] (fig. 2). Even with positive FDG-PET scan for months and years after SBRT, false-positive interpretation should be excluded by biopsy. Pneumonitis and pneumonia can pretend tumor progression, with SUV up to 7.

Future

While anatomical surgical resection has long been the standard treatment for stage I patients, SBRT could offer a less toxic, less costly, and more convenient alternative. With the promising preliminary results from single institutions, the maturing evaluation of late radiation toxicity, and the conduct of multicenter prospective trials in both operable and medically inoperable patients, SBRT shows considerable promise to be one of the most important recent innovations for effectively treating patients with primary and secondary lung cancer. However, prospective testing is required to insure that cure rates are not compromised. Clinical prospective phase II trials testing SBRT in operable patients is ongoing or planned in Japan (Japan Clinical Oncology Group, JCOG, protocol 0403) and the United States (Radiation Therapy Oncology Group, RTOG, protocol 0618), and a comparison of SBRT with surgery in the US. In medically inoperable patient groups, a Nordick multi-institutional consortium is comparing 3 fraction SBRT to conventional radiotherapy in an ongoing randomized phase II study. The RTOG has finished a phase II study of 3 fraction SBRT for peripheral tumors and is planning a phase I study with 5 fractions in patients with central tumors (RTOG 0633), and the JCOG is finishing a phase II study using a 4-fraction treatment for peripheral tumors and is planning a phase II study using a higher dose specifically for T2 tumors. Further trials in planning stages at the RTOG include the addition of targeted systemic therapies to SBRT (RTOG 0624) [12].

References

1 Kanavos P: The rising burden of cancer in the developing world. Ann Oncol 2006;17(suppl 8): viii15–viii23.

2 Alam N, Darling G, Shepherd FA, Mackay JA, Evans WK, Lung Cancer Disease Site Group of Cancer Care Ontario's Program in Evidence-Based Care: Postoperative chemotherapy in nonsmall cell lung cancer: a systematic review. Ann Thorac Surg 2006;81:1926–1936.

3 Bernstein ED, Herbert SM, Hanna NH: Chemotherapy and radiotherapy in the treatment of resectable non-small-cell lung cancer. Ann Surg Oncol 2006;13:291–301.
4 Mountain CF: The evolution of the surgical treatment of lung cancer. Chest Surg Clin N Am 2000;10:83–104.
5 Sugarbaker DJ, Strauss GM: Extent of surgery and survival in early lung carcinoma: implications for overdiagnosis in stage IA nonsmall cell lung carcinoma. Cancer 2000;89:S2432–S2437.
6 Reed MF, Molloy M, Dalton EL, Howington JA: Survival after resection for lung cancer is the outcome that matters. Am J Surg 2004;188:598–602.
7 Zimmermann FB, Bamberg M, Molls M, Jeremic B: Radiation Therapy Alone in Early Stage Non-small Cell Lung Cancer. Semin Surg Oncol 2003; 21:91–97.
8 Rosenzweig KE, Fox JL, Yorke E, Amols H, Jackson A, Rusch V, Kris MG, Ling CC, Leibel SA: Results of a phase I dose-escalation study using three-dimensional conformal radiotherapy in the treatment of inoperable nonsmall cell lung carcinoma. Cancer 2005;103:2118–2127.
9 Kong FM, Ten Haken RK, Schipper MJ, Sullivan MA, Chen M, Lopez C, Kalemkerian GP, Hayman JA: High-dose radiation improved local tumor control and overall survival in patients with inoperable/unresectable non-small-cell lung cancer: long-term results of a radiation dose escalation study. Int J Radiat Oncol Biol Phys 2005;63:324–333.
10 Bradley J, Graham MV, Winter K, Purdy JA Komaki R, Roa WH, Ryu JK, Bosch W, Emami B: Toxicity and outcome results of RTOG 9311:a phase I-II does-escalation study using three-dimensional conformal radiotherapy in patients with inoperable non-small-cell lung carcinoma. Int J Radiat Oncol Biol 2005;61:318–328.
11 Timmerman R, Abdulrahman R, Kavanagh BD, Meyer JL: Lung cancer: a model for implementing stereotactic body radiation therapy into practice; in Meyer JL (ed): IMRT, IGRT, SBRT – Advances in the Treatment Planning and Delivery of Radiotherapy. Front Radiat Ther Oncol. Basel, Karger, 2007, vol 40, pp 368–385.
12 Decker RH, Wilson LD: Advances in radiotherapy for lung cancer. Semin Respir Crit Care 2008;29:285–290.
13 Zimmermann FB, Geinitz H, Schill S, Grosu A, Schratzenstaller U, Molls M, Jeremic B: Stereotactic hypofractionated radiation therapy for stage I non-small cell lung cancer. Lung Cancer 2005;48: 107–114.
14 Beitler J, Badine EA, El-Sayah D, Makara D, Friscia P, Silverman P, Terjanian T: Stereotactic body radiation therapy for nonmetastatic lung cancer: an analysis of 75 patients treated over 5 years. Int J Radiat Oncol Biol Phys 2006;65:100–106.
15 Onishi H, Shirato H, Nagata Y, Hiraoka M, Fujino M, Gomi K, Niibe Y, Karasawa K, Hayakawa K, Takai Y, Kimura T, Takeda A, Ouchi A, Hareyama M, Kokubo M, Hara R, Itami J, Yamada K, Araki T: Hypofractionated stereotactic radiotherapy (HypoFXSRT) for stage I non-small cell lung cancer: updated results of 257 ptients in a Japanese multi-institutional study. J Thorac Oncol 2007;7: S94–S100.
16 Timmerman R, Bastasch M, Saha D, Abdulrahman R, Hittson W, Story M: Optimizing dose and fractionation for stereotactic body radiation therapy; in Meyer (ed): IMRT, IGRT, SBRT – Advances in the Treatment Planning and Delivery of Radiotherapy. Front Radiat Ther Oncol. Basel, Karger, 2007, vol 40, pp 352–365.
17 Lax I, Blomgren H, Naslund I, Svanstrom R: Stereotactic radiotherapy of malignancies in the abdomen: methodological aspects. Acta Oncol 1994;33:677–683.
18 Lax I, Blomgren H, Larson D, Näslund I: Extracranial stereotactic radiosurgery of localized targets. J Radiosurg 1998;1:135–148.
19 Timmerman R, Galvin J, Michalski J, Straube W, Ibbott G, Martin E, Abdulrahman R, Swann S, Fowler J, Choy H: Accreditation and quality assurance for Radiation Oncology Group: Multicenter clinical trials using stereotactic body radiation therapy in lung cancer. Acta Oncol 2006;45: 779–786.
20 ICRU 62: Prescription, Recording and Reporting Photon Beam Therapy. Bethesda, 1999.
21 El-Bayoumi E, Silvestri GA: Bronchoscopy for the diagnosis and staging of lung cancer. Semin Respir Crit Care Med 2008;29:261–270.
22 De Leyn P, Lardinois D, Van Schil PE, Rami-Porta R, Passlick B, Zielinski M, Waller DA, Lerut T, Weder W: ESTS guidelines for preoperative lymph node staging for non-small cell lung cancer. Eur J Cardio-Thorac Sur 2007;32:1–8.
23 Tanoue LT: Staging of non-small cell lung cancer. Semin Respir Crit Care Med 2008;29:248–260.

24 De Ruysscher D, Wanders S, van Haren E, Hochstenbag M, Geeraedts W, Utama I, Simons J, Dohmen J, Rhami A, Buell U, Thimister P, Snoep G, Boersma L, Verschueren T, van Baardwijk A, Minken A, Bentzen SM, Lambin P: Selective mediastinal node irradiation based on FDG-PET scan data in patients with non-small cell lung cancer: a prospective clinical study. Int J Radiat Oncol Biol Phys 2005;62:988–994.

25 Silvestri GA, Gould MK, Margolis ML, Tanoue LT, McCrory D, Toloza E, Detterbeck F: Noninvasive staging of non-small cell lung cancer. Chest 2007;132:S178–S201.

26 Yi CA, Shin KM, Lee KS, Kim H, Kim H, Kwon OJ, Choi JY, Chung MJ: Non-small cell lung cancer staging: efficacy comparison of integrated PET/CT versus 3.0-T whole-body MR imaging. Radiology 2008;248:632–642.

27 Blomgren H, Lax I, Naslund I, Svanstrom R: Stereotactic high dose fraction radiation therapy of extracranial tumors using an accelerator: clinical experience of the first thirty-one patients. Acta Oncol 1995;34:861–870.

28 Wulf J, Haedinger U, Oppitz U, Thiele W, Ness-Dourdoumas R, Flentje M: Stereotactic radiotherapy of targets in the lung and liver. Strahlenther Onkol 2001;177:645–655.

29 Lagerwaard F, Van Sornsen de Koste J, Nijssen-Visser M, Schuchard-Schippeer RH, Oei SS, Munne A, Senan S: Multiple 'slow' CT scans for incorporating lung tumor mobility in radiotherapy planning. Int J Radiat Oncol Biol Phys 2001; 51:932–937.

30 Guckenberger M, Meyer J, Wilbert J, Richter A, Baier K, Mueller G, Flentje M: Pulmonary injury and tumor response after stereotactic body radiotherapy (SBRT): Results of a serial follow-up CT study. Radiother Oncol 2007;85:435–442.

31 Baumann P, Nyman J, Lax I, Friesland S, Hoyer M, Rehn Ericsson S, Johansson KA, Ekberg , Morhed E, Paludan M, Wittgren L, Blomgren H, Lewensohn R: Factors important for efficacy of stereotactic body radiotherapy of medically inoperable stage I lung cancer: a retrospective analysis of patients treated in the Nordic countries. Acta Oncol 2006;45:787–795.

32 Zimmermann FB, Geinitz H, Schill S, Thamm R, Nieder C, Schratzenstaller U, Molls M: Stereotactic hypofractionated radiotherapy in stage I (T1–2 N0 M0) non-small cell lung cancer (NSCLC). Acta Oncol 2006;45:796–801.

33 Wulf J, Baier K, Mueller G, Flentje MP: Dose-response in stereotactic irradiation of lung tumors. Radiother Oncol 2005;77:83–87.

34 Hoyer M, Roed H, Traberg Hansen A, Ohlhuis L, Petersen J, Nellemann H, Kiil Berthelsen A, Grau C, Aage Engelholm S, von der Maase H: Phase II study on stereotactic body radiotherapy of colorectal metastases. Acta Oncol 2006;45:823–830.

35 Okunieff P, Petersen AL, Philip A, Milano MT, Katz AW, Boros L, Schell MC: Stereotactic body radiation therapy (SBRT) for lung metastases. Acta Oncol 2006;45:808–817.

36 Wurm RE, Gum F, Erbel S, Schlenger L, Scheffler D, Agaoglu D, Schild R, Gebauer B, Rogalla P, Plotkin M, Ocran K, Budach V: Image guided respiratory gated hypofractionated stereotactic body radiation therapy (H-SBRT) for liver and lung tumors: initial experience. Acta Oncol 2006; 45:881–889.

37 Hodge W, Tomé W, Jaradat HA, Orton NP, Khuntia D, Traynor A, Weigel T, Mehta MP: Feasibility report of image guided stereotactic body radiotherapy (IG-SBRT) with tomotherapy for early stage medically inoperable lung cancer using extreme hypofractionation. Acta Oncol 2006;45: 890–896.

38 Nuyttens JJ, Prevost JB, Praag J, Hoogeman M, van Klaveren RJ, Levendag PC, Pattynama PM: Lung tumor tracking during stereotactic radiotherapy treatment with the Cyberknife: marker placement and early results. Acta Oncol 2006;45:961–965.

39 Nagata Y, Takayama K, Matsuo Y, Norihisa Y, Mizowaki T, Sakamoto T; Sakamoto M, Mitsumori M, Shibuya K, Araki N, Yano S, Hiraoka M: Clinical outcomes of a phase I/II study of 48Gy of stereotactic body radiation therapy in 4 fractions using a stereotactic body frame. Int J Radiat Oncol Biol Phys 2005;63:1427–1431.

40 Hata M, Tokuuye K, Kagel K, Sugahara S, Nakayama H, Fukumitsu N, Hashimoto T, Mizumoto M, Ohara K, Akine Y: Hypofractionated high-dose proton beam therapy for stage I non-small cell lung cancer: preliminary results of a phase I/II clinical study. Int J Radiat Oncol Biol Phys 2007;68:786–793.

41 Panettieri V, Wennberg B, Gagliardi G, Duch MA; Ginjaume M, Lax I: SBRT of lung tumours: Monte Carlo simulation with PENELOPE of dose distributions including resiratory motion and comparison with different treatment planning systems. Phys Med Biol 2007;52:4265–4281.

42 Timmerman R, Papiez L, McGarry R, Likes L, DesRosiers C, Bank M, Frost S, Randall M, Williams M: Extracranial stereotactic radioablation: results of a phase I study in medically inoperable stage I non-small cell lung cancer. Chest 2003;124: 1946–1955.

43 Timmerman R, McGarry R, Yiannoutsos C, Papiez L, Tudor K, DeLuca J, Ewing M, Abdulrahman R, DeRosiers C, Williams M, Fletcher J: Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. J Clin Oncol 2006;24:4833–4839.

44 Park C, Papiez L, Zhang S, Story M, Timmerman RD: Universal survival curve and single fraction equivalent dose: useful tools in understanding potency of ablative radiotherapy. Int J Radiat Oncol Biol Phys 2008;70:847–852.

45 Uematsu M, Yamamoto F, Takai K, Ozeki Y, Tsumadori G, Aoki T, Tahara K, Shioda A, Fukui S, Kusano S: Stereotactic radiation therapy for primary or metastatic lung cancer: Preliminary experience with a linear accelerator-based treatment unit. Int J Radiat Oncol Biol Phys 1996; 36(suppl):352.

46 Nagata Y, Negoro Y, Aoki T, Mizowaki T, Takayama K, Kokubo M, Araki N, Mitsumori M, Sasai K, Shibamoto Y, Koga S, Yano S, Hiraoka M: Clinical outcomes of 3D conformal hypofractionated single high-dose radiotherapy for one or two lung tumors using a stereotactic body frame. Int J Radiat Oncol Biol Phys 2002;52:1041–1046.

47 Hof H, Muenter M, Oetzel D, Hoess A, Debus J, Herfarth K: Stereotactic single-dose radiotherapy (radiosurgery) of early stage nonsmall-cell lung cancer. Cancer 2007;110:148–155.

48 Uematsu M, Shioda A, Tahara K, Fukui T, Yamamoto F, Tsumatori G, Ozeki Y, Aoki T, Watanabe M, Kusano S: Focal, high dose, and fractionated modified stereotactic radiation therapy for lung carcinoma patients: a preliminary experience. Cancer. 1998;82:1062–1070.

49 Arimoto T, Usubuchi H, Matsuzawa T, Yonesaka A, Shimizu S; Shirato H, Miyasaka K: Small volume multiple non-coplanar arc radiotherapy for tumors of the lung, head and neck and the abdominopelvic region; in Lemke H, Vannier MW, Inamura K, Garman AG (eds): Computer Assisted Radiology and Surgery. Proc 12th Int Symp and Exhibition on Computer Assisted Radiology and Surgery. CARS '98 Tokyo, 1998. Elsevier Press, Amsterdam, 1998, pp 257–261.

50 Shirato H, Shimizu S, Tadashi S, Nishioka T, Miyasaka K: Real time tumour tracking radiotherapy. Lancet 1999;353:1331–1332.

51 Uematsu M, Shioda A, Suda A, Fukui T, Ozeki Y, Hama Y, Wong JR, Kusang S. computed tomography-guided frameless stereotactic radiotherapy for stage I non-small-cell lung cancer: a 5-year experience. Int J Radiat Oncol Biol Phys 2001;51:666–670.

52 Onimaru R, Shirato H, Shimizu S, Kitamura K, Xu B, Fukumoto S, Chang TC, Fujita K, Oita M, Miyasaka K, Nishimura M, Dosaka-Akita H: Tolerance of organs at risk in small-volume, hypofractionated, image-guided radiotherapy for primary and metastatic lung cancers. Int J Radiat Oncol Biol Phys 2003;56:126–135.

53 Wulf J, Haedinger U, Oppitz U, Thiele W, Mueller G, Flentje M: Stereotactic radiotherapy for primary lung cancer and pulmonary metastases: a noninvasive treatment approach in medically inoperable patients. Int J Radiat Oncol Biol Phys 2004;60:186–196.

54 Nyman J, Johansson KA, Hulten U: Stereotactic hypofractionated radiotherapy for stage I nonsmall cell lung cancer: mature results for medically inoperable patients. Lung Cancer 2006;51: 97–103.

55 Xia T, Li H, Sun Q, Wang Y, Fan N, Yu Y, Li P, Chang JY: Promising clinical outcome of stereotactic body radiation therapy for patients with inoperable Stage I/II non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2006;66:117–125.

56 Hara R, Itami J, Kondo T, Aruga T, Uno T, Sasano N, Onishi K, Kiyozuka M, Fuse M, Ito M, Naoi K, Kohno Y: Clinical outcomes of single-fraction stereotactic radiation therapy of lung tumors. Cancer 2006;106:1347–1352.

57 Timmerman RD, Park C, Kavanagh BD: The North American experience with stereotactic body radiation therapy in non-small cell lung cancer. J Thorac Oncol 2007;2:S101–S112.

58 Fritz P, Kraus HJ, Blaschke T, Mühlnickel W, Strauch K, Engel-Riedel W, Chemaissani A, Stoelben E: Stereotactic, high single-dose irradiation of stage I non-small cell lung cancer (NSCLC) using four-dimensional CT scans for treatment planning. Lung Cancer 2008;60:193–199.

59 Ng AW, Tung SY, Wong VY: Hypofractionated stereotactic radiotherapy for medically inoperable stage I non-small cell lung cancer: report on clinical outcome and dose to critical organs. Radiother Oncol 2008;87:24–28.

60 Onimaru R, Fujino M, Yamazaki K, Onodera Y, Taguchi H, Katoh N, Hommura F; Oizumi S, Nishimura M, Shirato H: Steep-dose-response relationship for stage I non-small-cell lung cancer using hypofractionated high-dose irradiation by real-time tumor-tracking radiotherapy. Int J Radiat Oncol Biol Phys 2008;70:374–381.

61 McCammon R, Schefter TE, Gaspar LE, Zaemisch R, Gravdahl D, Kavanagh B: Observation of a dose-control relationship for lung and liver tumors after stereotactic body radiation therapy. Int J Radiat Oncol Biol Phys 2009;73:112–118.

62 Salazar OM, Sandhu TS, Lattin PB, Chang JH, Lee CK, Groshko GA, Lattin CJ: Once-weekly, high-dose stereotactic body radiotherapy for lung cancer: 6-year analysis of 60 early-stage, 42 locally advanced, and 7 metastatic lung cancers. Int J Radiat Oncol Biol Phys 2008;72:707–715.
63 Takeda A, Sanuki N, Kunieda E, Ohashi T, Oku Y, Takeda T, Shigematsu N, Kubo A: Stereotactic body radiotherapy for primary lung cancer at a dose of 50 Gy total in five fractions to the periphery of the planning target volume calculated using a superposition algorithm. Int J Radiat Oncol Biol Phys 2009;73:442–448.
64 Brown WT, Wu X, Wen BC, Fowler JF, Fayad F, Amendola BE, Garcia S, De La Zerda A, Huang Z, Schwade JG: Early results of CaberKnife image-guided robotic stereotactic radiosurgery for treatment of lung tumors. Comp Aided Surg 2007;12: 253–261.
65 Lee S, Choi EK, Park HJ, Ahan SD, Kim JH, Kim KJ, Yoon SM, Kim YS, Yi BY: Stereotactic body frame based fractionated radiosurgery in the consecutive days for primary and metastatic tumor in the lung. Lung Cancer 2003;40:309–315.
66 Timmerman RD, Park C, Kavanagh BD: The North American experience with stereotactic body radiation therapy in non-small cell lung cancer (appendix). J Thorac Oncol 2007;2:S101–S112.
67 Collins BT, Vahdat S, Erickson K, Collins SP, Suy S, Yu X, Zhang Y, Subramaniam D, Reichner CA, Sarikaya I, Esposito G, Yousefi S, Jamis-Dow C, Banovac F, Anderson ED: Radical cyberknife radiosurgery with tumor tracking: an effective treatment for inoperable small peripheral stage I non-small cell lung cancer. J Hematol Oncol 2009; 2:1–9.
68 Pennathur A, Luketich JD, Heron DE, Abbas G, Burton S, Chen M, Gooding WE, Ozhasoglu C, Landreneau RJ, Christie NA: Stereotactic radiosurgery for the treatment of stage I non-small cell lung cancer in high-risk patients. J Thorac Cardiovasc Surg 2009;137:597–604.
69 Koenig TR, Kunden RF, Erasmus JJ, Sabloff BS, Gladish GW, Komaki R, Stevens CW: Radiation injury of the lung after three-dimensional conformal radiotherapy. AJR 2002;178:1383–1388.
70 Aoki T, Nagata Y, Negoro Y, Takayama K, Mizowaki T, Kokubo M, Oya N, Mitsumori M, Hiraoka M: Evaluation of lung injury after three-dimensional conformal stereotactic radiotherapy for solitary lung tumors. Radiology 2004;230:101–108.
71 Takeda T, Takeda A, Kunieda E, Ishizaka A, Takemasa K, Shimado j, Yamamoto S, Shigematsu N, Kawaguchi O, Fukada J, Ohashi T, Kuribayashi S, Kubo A: Radiation injury after hypofractionated stereotactic radiotherapy for peripheral small lung tumors: serial changes on CT. AJR 2004; 182:1123–1128.
72 Inoue T, Shimizu S, Onimaru RE, Takeda A, Onishi H, Nagata Y, Kimura T, Karasawa K, Arimoto T, Hareyama M, Kikuchi E, Shirato H: Clinical outcomes of stereotactic body radiotherapy for small lung lesions clinically diagnosed as primary lung cancer on radiologic examination. Int J Radiat Oncol Biol Phys 2009;in press.
73 McGarry RC, Papiez L, Williams M, Whitford T, Timmerman RD: Stereotactic body radiation therapy of early stage non-small cell lung cancer: phase I study. Int J Radiat Oncol Biol Phys 2005; 63:1010–1015.
74 Joyner M, Salter BJ, Papanikolaou N, Fuss M: Stereotactic body radiation therapy for centrally located lung lesions. Acta Oncol 2006;45:802–807.

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Phase I trial of combination chemotherapy with docetaxel, cisplatin and S-1 (TPS) in patients with locally advanced or recurrent/metastatic head and neck cancer

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Background: We investigated the maximum tolerated dose (MTD) of combination therapy with docetaxel, cisplatin, and S-1 (TPS) in patients with locally advanced or recurrent/metastatic head and neck cancer (HNC).

Patients and methods: Treatment consisted of docetaxel (Taxotere) at doses of 50, 60, and 70 mg/m^2; cisplatin at 70 mg·m^2/day on day 1; and S-1 twice daily on days 1–14 at doses of 40, 60, and 80 mg·m^2/day, repeated every 3 or 4 weeks.

Results: Forty patients were enrolled. MTD was not reached until level 4. Subjects at expanded dose were limited to patients with locally advanced disease. Two dose-limiting toxic effects (DLTs) were observed at dose level 5 (TPS: 70/70/80 mg·m^2/day, every 3 weeks), namely one grade 3 infection and one grade 3 hyperbilirubinemia, establishing this as the MTD. Of 12 patients treated at dose level 6 (TPS: 70/70/60 mg·m^2/day, every 3 weeks), 2 DLTs were seen. Six achieved a complete response and 22 a partial response, giving a response rate of 70%.

Conclusions: TPS was well tolerated. The recommended phase II dose as induction chemotherapy for locally advanced HNC was determined as 70/70/60 mg·m^2/day every 3 weeks. Antitumor activity was highly promising and warrants further investigation.

Key words: cisplatin, docetaxel, head and neck cancer, S-1

introduction

Head and neck cancers (HNCs) are the sixth most common cancer in the world, and ~500 000 new cases are projected annually [1]. An estimated 60% of these patients will present with locally advanced disease (stage III/IV).

Platinum-based chemotherapy is widely used for recurrent/metastatic HNC. The combination of docetaxel, cisplatin, and 5-fluorouracil (5-FU) (TPF) has been considered the standard regimen for induction chemotherapy for locally advanced squamous cell carcinoma of the head and neck (SCCHN) [2, 3]. Nevertheless, this combination is stressful to patients, and the continuous infusion of 5-FU in this combination reduces quality of life, owing not only to toxicity but also to inconvenience and catheter-related complications. Other options with improved safety profiles and greater convenience are thus highly desirable.

In response to this need, one growing trend has been the substitution of conventional 5-FU with the oral prodrug of 5-FU. S-1 is a novel oral fluoropyrimidine derivative, which consists of tegafur, gimeracil (5-chloro-2, 4-dihydrogenase; CDHP), and potassium oxonate (Oxo) at a molar ration of 1 : 0.4 : 1 [4]. Tegafur is a prodrug of 5-FU. CDHP augments the activity of 5-FU by inhibiting dihydropyrimidine dehydrogenase. Oxo reduces gastrointestinal (GI) toxicity by inhibiting orotate phosphoribosyl transferase and 5-FU phosphorylation in intestinal mucosa [5].

S-1 has shown activity against HNC, producing a response rate of 34% [6]. A combination of cisplatin and S-1 shows promising efficacy (response rate: 67.6%) with acceptable toxicity for locally advanced HNC [7]. Furthermore, a combination of docetaxel and S-1 has demonstrated promising efficacy with acceptable toxicity for many cancers [8–11].

Based on these promising results, we speculated that replacing 5-FU with S-1 in combination with docetaxel and cisplatin would be a reasonable alternative to continuous

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infusion of 5-FU. To our knowledge, however, combination therapy with docetaxel, cisplatin, and S-1 (TPS) in the treatment of HNC has not been investigated.

Here, we conducted a phase I study of a combination therapy with TPS in patients with locally advanced or recurrent/metastatic HNC.

patients and methods

eligibility criteria

All patients had a histologically or cytologically confirmed diagnosis of HNC with recurrent/metastatic or unresectable locally advanced disease. Eligibility also required an Eastern Cooperative Oncology Group performance status of zero or one, age 20–75 years, and adequate organ function. Written informed consent was required from all patients before the start of study therapy.

Patients were excluded for any of the following conditions: history of prior chemotherapy; concurrent active malignancy except excised intramucosal gastric or esophageal cancer, which could be removed by endoscopic mucosal resection; pharyngeal fistula; active bleeding from the GI tract; active infection; serious medical problem that might interfere with the achievement of study objectives; pregnancy or lactation; or expected survival of <3 months.

The study was approved by the Institutional Review Board at the National Cancer Center.

study design

The study was conducted as an open-label, single arm, phase I, single-institution dose-escalation study aimed at testing the safety of combination therapy with TPS in patients with locally advanced or recurrent/metastatic HNC. A total of six dose combinations were planned (Table 1).

Toxic effects were evaluated according to National Cancer Institute—Common Toxicity Criteria for Adverse Events version 2.0. A minimum of three assessable patients was treated at each dose level. If one of the three patients at a given dose level experienced a dose-limiting toxicity (DLT), three additional patients were accrued at the same dose level. The maximum tolerated dose (MTD) was defined as the dose at which two or more patients of six experienced a DLT. After the MTD was determined, three more patients were treated at the next lower dose level. If no or only one of the six patients experienced a DLT, an additional six patients were accrued at the same dose level to determine the recommended dose (RD). No intra-patient dose escalation was allowed.

DLT was defined as any of the following adverse events occurring within 30 days after completion of the first cycle of TPS: (i) febrile neutropenia lasting >4 days; (ii) grade 4 thrombocytopenia (<10 000/mm^3); (iii) grade 4 vomiting; (iv) grade 3 or 4 nonhematological toxic effects except grade 3 anorexia, nausea, vomiting, stomatitis, esophagitis, and infection due to stomatitis; (v) cessation of treatment due to an adverse event; or (vi) treatment-related death.

treatment

Chemotherapy consisted of a 1-h infusion of docetaxel at escalating doses of 50, 60, and 70 mg/m^2; a 2-h infusion of cisplatin at 70 mg·m^2/day on day 1; and S-1 twice daily on days 1–14 at escalating doses of 40, 60, and 80 mg·m^2/day. This regimen was repeated every 3 or 4 weeks. Prophylactic use of granulocyte colony-stimulating factor was not allowed but ciprofloxacin was administered on days 5 through 15.

The dose escalation schema is depicted in Table 1. At dose levels 1–4, treatment was repeated every 4 weeks, with a maximum of six cycles allowed until unacceptable toxicity, patient refusal or disease progression was observed. At dose levels 5 and 6, the subject had to have locally advanced HNC and to have received TPS every 3 weeks with a maximum of three cycles allowed. Patients with locally advanced HNC who recorded a response after completion of three cycles of TPS were able to receive definitive treatment, including concurrent chemoradiotherapy.

treatment evaluation and dose modifications

Baseline evaluation consisted of history, physical examination, radiographic imaging, routine laboratory studies, and electrocardiogram. Safety assessments were repeated weekly after the start of chemotherapy.

Doses were modified in case of severe hematological or nonhematological toxic effects. Since patients received three chemotherapeutic agents, dose adjustment was carried out for each individual agent based on its estimated causal relationship to the toxicity; if multiple agents were felt to be causing the toxicity, dose reduction was carried for multiple agents according to the RD reduction schedule below. If multiple toxic effects occurred during a treatment cycle, the toxicity with the highest grade was used as the parameter for dose adjustment.

Grade 4 hematological toxic effects or grade 3 infection required a dose reduction of all three drugs. Grade 3 diarrhea, mucositis, or skin reaction required a reduction in S-1 dose. Grade 2 neurotoxicity required a reduction in cisplatin dose. Grade 3 neurotoxicity required the discontinuation of cisplatin. Creatinine clearance (CCr) was calculated at the beginning of each cycle according to the Cockcroft–Gault formula. CCr values >60 ml/min required no dose modification; those from 50 to <60 ml/min required a reduction in both S-1 and cisplatin by one dose level; those from 40 to <50 ml/min required a reduction of both S-1 and cisplatin by two dose levels; and those <40 ml/min required the cessation of both S-1 and cisplatin. Patients were removed from treatment if more than two dose reductions were required or if there was a treatment delay of >21 days due to toxicity.

Tumors responses were evaluated according to RECIST.

Table 1. Dose escalation schema and DLTs

1	50	70	40	4	R/M and LA	0/4	
2	60	70	40	4	R/M and LA	0/3	
3	60	70	60	4	R/M and LA	0/3	
4	60	70	80	4	R/M and LA	1/12	Grade 3 infection
5	70	70	80	3	LA	2/6	Grade 3 infection, grade 3 hyperbilirubinemia
6	70	70	60	3	LA	2/12	Grade 3 diarrhea, grade 3 ALT/AST↑

ALT, alanine aminotransferase; AST, aspartate aminotransferase; DLT, dose-limiting toxicity; LA, locally advanced disease; R/M, recurrent/metastatic disease.

end points and statistical methods

The primary end point in this study was the MTD and RD of this regimen. Secondary end points included the safety and tolerability of this combination and relative dose intensity and efficacy, including response rate, progression-free survival (PFS), and overall survival (OS).

Relative dose intensity was calculated as the ratio of the actual to planned dose intensity in milligrams per square meter per week. The survival curve was estimated using the Kaplan–Meier method. Safety and efficacy analyses were both conducted on an intention-to-treat (ITT) population, defined as all patients enrolled in the study who received at least one dose of chemotherapy. A subject's PFS was defined as the time from the date of the first administration of chemotherapy to the first documentation of disease progression, subsequent therapy, or death. OS was determined from the date of the first administration of chemotherapy to the date of death or the last confirmation of survival. Statistical data were obtained using the SPSS software package (SPSS 11.0 Inc., Chicago, IL).

results

patient and disease characteristics

From November 2004 to September 2008, a total of 40 patients were enrolled, consisting of 33 males and 7 females with a median age of 50 years (range 22–74 years). Patient characteristics in the ITT population are listed in Table 2.

Table 2. Patient characteristics

Characteristic	No. of patients (n = 40)
Age, years	
Median	50
Range	22–74
Sex	
Male	33
Female	7
Eastern Cooperative Oncology Group performance score	
0	35
1	5
Site of primary tumor	
Hypopharynx	9
Oral cavity	1
Oropharynx	10
Salivary gland	3
Nasopharynx	13
Nasal cavity	3
Histology	
Squamous cell carcinoma	23
Adenoid cystic carcinoma	3
Undifferentiated carcinoma	9
Others	5
Disease status	
Recurrent/metastatic disease	11
Locally advanced disease	29
Prior treatment	
None	31
Surgery alone	4
Surgery with adjuvant radiotherapy	1
Radiotherapy alone	4

Twenty-nine cases were locally advanced cancer and 11 were recurrent/metastatic cancer.

treatment administration

A total of 116 cycles was administered (median = 3, range 1–6) over six dose levels. Twenty cycles required dose reduction, while six required a delay of >7 days due to toxicity. Six patients discontinued treatment due to disease progression and two due to treatment-related toxicity, while two other patients refused further treatment due to fatigue. Three of 11 patients with recurrent/metastatic disease completed six cycles of TPS as a palliative chemotherapy, whereas 27 of 29 patients with locally advanced disease completed three cycles of TPS as induction chemotherapy. Twenty-four patients received subsequent chemoradiotherapy concurrently with cisplatin (cisplatin 20 mg/m^2, i.v., days 1–4, days 22–25, days 43–46) after completion of TPS. One patient received chemoradiotherapy with 5-FU plus cisplatin (5-FU 400 mg/m^2, i.v., days 1–5, days 29–33, cisplatin 20 mg/m^2, i.v., days 1–4, days 29–32). Four patients received proton beam therapy concurrently with cisplatin at the same schedule as chemoradiotherapy. One patient for whom no response was documented after two cycles of TPS received palliative chemoradiotherapy. Median total dose of photon therapy and proton beam therapy was 70 Gy (range 66–70) and 70 Gy (range 65–70), respectively.

dose escalation and DLT

DLTs are listed in Table 1. No DLTs were observed until dose level 3. At dose level 4, one patient experienced grade 3 infection, leading cohort expansion, but no further DLTs were observed at this dose level. Although MTD was not reached by this level, further escalation was not initially planned. An additional six patients were accrued at this level to determine the RD. Since MTD was not reached by dose level 4 and the dose intensities of docetaxel and cisplatin at this level (docetaxel 15 mg·m^2/week, cisplatin 17.5 mg·m^2/week) were markedly lower than that of previous studies of induction TPF for locally advanced HNC (docetaxel 25 mg·m^2/week, cisplatin 25 mg·m^2/week), we amended the protocol to include a dose escalation of docetaxel and shortening of treatment cycle and limited the subjects to patients with locally advanced disease. In other words, MTD was evaluated at dose level 5 or 6 to determine the RD of TPS as induction chemotherapy for locally advanced HNC.

At dose level 5, two DLTs were observed, namely one grade 3 infection and one grade 3 hyperbilirubinemia, establishing this as the MTD. The relative dose intensity at this dose level was 0.67 (range 0.40–0.85). In the 12 patients at dose level 6, two DLTs were observed, namely one grade 3 elevation of alanine aminotransferase/aspartate aminotransferase and one grade 3 diarrhea. The relative dose intensity at this dose level was 0.92 (range 0.41–1.0). Based on the results, the RD of this combination was determined as docetaxel 70 mg/m^2, cisplatin 70 mg/m^2, and S-1 60 mg/m^2 for 14 days, every 3 weeks.

toxicity

Overall toxic effects during TPS administration are listed in Table 3. Grade 3 or 4 hematological toxic effects are listed by

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dose level in Table 4. At dose level 5, all patients experienced grade 4 neutropenia. Grade 2 or 3 nonhematological toxic effects are listed by dose level in Table 5. No grade 4 nonhematological toxic effects were observed during any course.

Major common grade 3 or 4 toxic effects in patients with locally advanced disease during chemoradiotherapy or proton beam therapy were mucositis (48%), dysphagia (34%), leucopenia (28%), anemia (17%), dermatitis (17%), and neutropenia (14%). Toxicity was as expected and manageable.

Table 3. Overall toxicity during TPS administration ($n = 40$)

Hematological toxicity					
Leucopenia	6	20	12	0	30
Neutropenia	6	9	12	12	60
Febrile neutropenia	0	0	5	0	13
Anemia	22	14	3	0	8
Thrombocytopenia	15	2	0	0	0
Nonhematological toxicity					
Nausea	16	14	1	0	3
Vomiting	12	3	0	0	0
Anorexia	15	14	6	0	15
Fatigue	13	7	0	0	0
Mucositis	5	3	1	0	3
Diarrhea	6	3	1	0	3
Elevated bilirubin	5	12	1	0	3
Elevated AST	14	3	1	0	3
Elevated ALT	10	6	1	0	3
Elevated creatinine	6	1	1	0	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

treatment outcomes

Efficacy data are listed in Table 6. All patients enrolled in this study were assessable for response to TPS. There were 6 complete and 22 partial responses, giving an overall response rate of 70% [95% confidence interval (CI) 59.1–80.8], broken down as 4 complete and 18 partial responses in the 29 patients with locally advanced disease, and 2 complete and 4 partial responses in the 11 with recurrent/metastatic disease. One of these latter two complete responders, who had residual disease after completion of radiotherapy for poorly differentiated squamous cell carcinoma of the nasopharynx, achieved a complete response after receiving three cycles of TPS without further treatment and remains alive without evidence of recurrence as of ~5 years later. Another patient, who had previous radiotherapy for undifferentiated carcinoma of the nasopharynx and multiple mediastinal lymph node metastases 4 months after receiving lobectomy for lung metastasis, achieved a complete response after completion of six cycles of TPS followed by S-1 alone for 2 years and is alive without evidence of disease progression as of >4 years after treatment. Although no objective response was observed in patients with adenoid cystic carcinoma, eight of nine patients with undifferentiated carcinoma achieved an objective response.

Of the 29 patients with locally advanced disease, 23 (79%; 95% CI, 64% to 93%) experienced complete remission after completion of definitive chemoradiotherapy or proton beam

Table 4. Grade 3 or 4 hematological toxicity during TPS administration by dose level

Leucopenia	1	0	0	0	0	0	3	0	5	0	1	0
Neutropenia	0	1	0	0	0	0	5	0	0	6	5	4
Febrile neutropenia	0	0	0	0	0	0	0	0	1	0	4	0
Anemia	0	0	0	0	0	0	0	0	0	0	0	0
Thrombocytopenia	0	0	0	0	0	0	0	0	0	0	0	0

Table 5. Grade 2 or 3 nonhematological toxicity during TPS administration by dose level

Anorexia	0	0	2	0	0	1	6	2	3	0	3	3
Nausea	1	0	0	0	1	0	5	1	2	0	4	0
Mucositis	0	0	0	0	2	0	1	1	0	0	0	0
Diarrhea	0	0	0	0	0	0	1	0	2	0	0	1
Infection	0	2	0	0	0	0	0	1	0	1	0	3

Table 6. Efficacy ($n = 40$)

Subset	No. of patients					%	
	CR	PR	SD	PD	NE	RR	95% CI
All ($n = 40$)	6	22	10	1	1	70	59.1–80.8
Disease status							
LA ($n = 29$)	4	18	6	1	0	76	62.2–89.8
R/M ($n = 11$)	2	4	4	0	1	55	38.7–71.2
Histology							
SCC ($n = 23$)	3	15	4	1	0	78	56.3–92.5
ACC ($n = 3$)	0	0	3	0	0	0	0–70.8
Undiff ($n = 9$)	2	6	1	0	0	89	51.8–99.7
Others ($n = 5$)	1	1	2	0	1	40	5.3–85.3

ACC, adenoid cystic carcinoma; CI, confidence interval; CR, complete response; LA, locally advanced disease; NE, not evaluated; PD, progressive disease; PR, partial response; RR, response rate; R/M, recurrent/metastatic disease; SCC, squamous cell carcinoma; SD, stable disease; Undiff, undifferentiated carcinoma.

therapy. Three patients achieved a partial response and the remaining three patients showed progressive disease, including bone metastasis ($n = 2$). With a median follow-up time of 19 months (range 6–52 months), locoregional recurrence and distant metastasis were observed in nine and four patients, respectively. A total of six patients died due to disease progression. Although the patient population was heterogeneous, the estimated 1-year PFS and OS in all patients were 64% and 85%, respectively. The estimated 1-year PFS in patients with recurrent/metastatic and locally advanced disease were 33% and 74%, respectively.

discussion

The past 5–10 years has seen an increasing trend for the substitution of conventional 5-FU with oral prodrugs of 5-FU, including S-1 and capecitabine, in chemotherapy regimens. Two randomized trials for advanced gastric cancer evaluated the safety and efficacy of S-1 compared with that of 5-FU: in one trial, S-1 showed statistically significant noninferiority to 5-FU ($P < 0.001$) [12], while in another trial [13], S-1 plus cisplatin was statistically noninferior to 5-FU plus cisplatin and had a significantly superior safety profile. These randomized trials have identified S-1 as a valuable substitute for bolus or infusional 5-FU in the treatment of gastric cancer.

Three trials of TPS in the treatment of advanced gastric cancer have been reported [14–16]. Given recognition in Japan that S-1 is a key drug in the treatment of gastric cancer, S-1 dose was fixed (S-1 80 mg·m^2/day on days 1–14) in all three trials, whereas dose intensities of docetaxel and cisplatin were markedly lower (docetaxel 10 or 20 mg·m^2/week, cisplatin 17.5 or 20 mg·m^2/week) than those of the standard TPF regimen (docetaxel 25 mg·m^2/week, cisplatin 25 mg·m^2/week) for SCCHN [2, 3]. Given the outcomes of the TAX 323 and TAX324 studies [2, 3], which demonstrated that, in addition to cisplatin, docetaxel is a key drug in the treatment of SCCHN, these TPS regimens would therefore not be appropriate substitutes for TPF in the treatment of SCCHN.

In contrast to the situation for gastric cancer, no randomized trial has compared S-1 with 5-FU for HNC and no previous studies have investigated TPS in the treatment of HNC. The present study is thus the first trial of TPS in the treatment of HNC. Results showed that the incidence of hematological toxic effects was comparable to that in TAX 323 and TAX324, whereas no grade 4 nonhematological toxic effects or treatment-related deaths were seen. At dose level 5 (docetaxel 70 mg/m^2, cisplatin 70 mg/m^2, and S-1 80 mg/m^2, every 3 weeks), two DLTs were observed, establishing this as the MTD. All patients at this level experienced grade 4 neutropenia and the relative dose intensity was 0.67, suggesting that this dose would not be feasible. At dose level 6 (docetaxel 70 mg/m^2, cisplatin 70 mg/m^2, and S-1 60 mg/m^2, every 3 weeks), 2 of 12 patients developed DLTs and the relative dose intensity at this dose level was 0.92, suggesting the feasibility of this dose as the RD of a phase II trial.

The rate of treatment-related death with the most widely accepted standard TPF regimen is 2.3% [2]. This is of concern, given that the goal of treatment for patients with locally advanced SCCHN is cure. Although the docetaxel and cisplatin doses at dose level 6 (docetaxel 70 mg/m^2, cisplatin 70 mg/m^2, and S-1 60 mg/m^2, every 3 weeks) were slightly lower than those with standard TPF, the incidence of febrile neutropenia (33%) was higher than that with standard TPF (5.2%), suggesting that further dose escalation may increase the risk of the treatment-related death. Hence, no further dose escalation was undertaken.

Many patients with locally advanced HNC experience dysphagia due to the primary tumor, and difficulty in swallowing capsules containing S-1 may be problematic. Nutritional support via feeding tube replacement in these patients is indispensable. Our previous pharmacokinetic findings showed that administration of S-1 as a suspension via a feeding tube was interchangeable with oral administration of whole capsules [17]. S-1 can therefore be administered to all HNC patients regardless of difficulty in swallowing capsules.

Although efficacy was not a primary end point of this study, antitumor activity (overall response rate 70%) was highly promising. Moreover, both patients with recurrent/metastatic nasopharyngeal cancer achieved a complete response after treatment, and remain alive and without recurrence at >4 years post-treatment. Although the number of patients was small and nasopharyngeal cancer is more sensitive to chemotherapy than other primary sites of HNC, antitumor activity was noteworthy. Furthermore, toxic effects during definitive therapy were relatively mild compared with those in previous studies of concurrent chemoradiotherapy for locally advanced SCCHN, suggesting that three cycles of TPS would not compromise the delivery of subsequent chemoradiotherapy.

During dose levels 1–4, this study included patients with recurrent/metastatic disease. If TPS had shown feasible and promising efficacy in these patients, this would have been encouraged further investigation to establish a new standard of care in the treatment of recurrent/metastatic SCCHN. Of 11 patients with recurrent/metastatic disease, however, 2 refused further treatment due to fatigue, even though they had achieved a clinical response and experienced no severe toxic effects, and almost all had limited treatment options if they had proved refractory to this combination. We therefore excluded patients with recurrent/metastatic disease from receiving dose levels 5

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and 6. Recently, the addition of cetuximab to platinum-based chemotherapy was shown to significantly prolong OS without exacerbating chemotherapy-associated toxicity or quality of life in patients with recurrent/metastatic SCCHN [18]. The addition of molecular-targeted drugs such as cetuximab to platinum-based chemotherapy would therefore be more feasible and appropriate than that of docetaxel to platinum-based chemotherapy in the treatment of recurrent/metastatic SCCHN.

Concern has been expressed over the considerable ethnic differences in the tolerated doses of S-1. These relate to the varying efficiency rates of conversion of tegafur to 5-FU by CYP2A6 of the CYP450 enzyme system, now identified as the principal enzyme responsible for this conversion process [19–22]. A phase I study of S-1 plus cisplatin in Western patients with advanced gastric carcinoma showed that the S-1 dose tolerated by Western patients is lower than that by Japanese patients but that the area under the curve of 5-FU appears higher in white than Japanese patients in a comparable dose range of S-1 [23]. This is mostly attributed to different polymorphisms in the *CYP2A6* gene among Asians and whites. The RD of the present study is likely unsuitable for Western patients, and further study to determine the RD of TPS for these patients is required. Moreover, further study of the present TPS should be done in Asian patients to clarify whether TPS is superior to TPF.

In conclusion, we found that treatment with TPS was well tolerated and feasible in patients with locally advanced HNC. This regimen demonstrated sufficient activity to warrant phase II testing and may be an optimal substitute for TPF in the treatment of locally advanced SCCHN. A randomized trial comparing TPS with TPF in patients with locally advanced SCCHN is warranted.

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disclosure

None of the authors declare conflicts of interest.

references

1. Parkin DM, Pisani P, Ferlay J. Estimates of the worldwide incidence of 25 major cancers in 1990. Int J Cancer 1999; 80: 827–841.
2. Vermorken JB, Remenar E, van Herpen C et al. Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer. N Engl J Med 2007; 357: 1695–1704.
3. Posner MR, Hershock DM, Blajman CR et al. Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. N Engl J Med 2007; 357: 1705–1715.
4. Shirasaka T, Shimamato Y, Ohshimo H et al. Development of a novel form of an oral 5-fluorouracil derivative (S-1) directed to the potentiation of the tumor selective cytotoxicity of 5-fluorouracil by two biochemical modulators. Anticancer Drugs 1996; 7: 548–557.
5. Shirasaka T, Shimamoto Y, Fukushima M. Inhibition by oxonic acid of gastrointestinal toxicity of 5-fluorouracil without loss of its antitumor activity in rats. Cancer Res 1993; 53: 4004–4009.
6. Inuyama Y, Kida A, Tsukuda M et al. [Late phase II study of S-1 in patients with advanced head and neck cancer]. Gan To Kagaku Ryoho 2001; 28: 1381–1390.
7. Fujii M. [Combination therapy with S-1 and CDDP for head and neck cancer]. Gan To Kagaku Ryoho 2006; 33 (Suppl 1): 150–154.
8. Yoshida K, Ninomiya M, Takakura N et al. Phase II study of docetaxel and S-1 combination therapy for advanced or recurrent gastric cancer. Clin Cancer Res 2006; 12: 3402–3407.
9. Tsutani Y, Ohara M, Suzuki T et al. Docetaxel and S-1 as a first-line treatment in patients with advanced or recurrent gastric cancer. Anticancer Res 2009; 29: 2775–2779.
10. Atagi S, Kawahara M, Kusunoki Y et al. Phase I/II study of docetaxel and S-1 in patients with previously treated non-small cell lung cancer. J Thorac Oncol 2008; 3: 1012–1017.
11. Ozaki T, Tamura K, Satoh T et al. Phase I study of combination therapy with S-1 and weekly docetaxel for advanced gastric cancer. Anticancer Res 2007; 27: 2657–2665.
12. Boku N, Yamamoto S, Fukuda H et al. Fluorouracil versus combination of irinotecan plus cisplatin versus S-1 in metastatic gastric cancer: a randomised phase 3 study. Lancet Oncol 2009; 10: 1063–1069.
13. Ajani JA, Rodriguez W, Bodoky G et al. Multicenter phase III comparison of cisplatin/S-1 with cisplatin/infusional fluorouracil in advanced gastric or gastroesophageal adenocarcinoma study: the FLAGS trial. J Clin Oncol 2010; 28: 1547–1553.
14. Nakayama N, Koizumi W, Sasaki T et al. A multicenter, phase I dose-escalating study of docetaxel, cisplatin and S-1 for advanced gastric cancer (KDOG0601). Oncology 2008; 75: 1–7.
15. Takayama T, Sato Y, Sagawa T et al. Phase I study of S-1, docetaxel and cisplatin combination chemotherapy in patients with unresectable metastatic gastric cancer. Br J Cancer 2007; 97: 851–856.
16. Fushida S, Fujimura T, Oyama K et al. Feasibility and efficacy of preoperative chemotherapy with docetaxel, cisplatin and S-1 in gastric cancer patients with para-aortic lymph node metastases. Anticancer Drugs 2009; 20: 752–756.
17. Tahara M, Minami H, Kawada K et al. Phase I trial of concurrent chemoradiotherapy with S-1 and CDDP in patients with unresectable locally advanced squamous cell carcinoma of the head and neck(SCCHN). In 3rd International Conference on Cancer Therapeutics, Edition (Abstr 105). Tokyo, Japan 2006.
18. Herrero FR, Hitt R, Kawecki A et al. Cetuximab plus platinum-based therapy first line in patients with recurrent/metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN): a quality of life (QOL) analysis of the EXTREME trial. In 33rd ESMO Congress, Edition: Annals of Oncology; 219 (Abstr 693PD). Stockholm, Sweden 2008.
19. van der Weide J, Steijns LS. Cytochrome P450 enzyme system: genetic polymorphisms and impact on clinical pharmacology. Ann Clin Biochem 1999; 36 (Pt 6): 722–729.
20. Yoshida R, Nakajima M, Nishimura K et al. Effects of polymorphism in promoter region of human CYP2A6 gene (CYP2A6*9) on expression level of messenger ribonucleic acid and enzymatic activity in vivo and in vitro. Clin Pharmacol Ther 2003; 74: 69–76.
21. Daigo S, Takahashi Y, Fujieda M et al. A novel mutant allele of the CYP2A6 gene (CYP2A6*11) found in a cancer patient who showed poor metabolic phenotype towards tegafur. Pharmacogenetics 2002; 12: 299–306.
22. Ikeda K, Yoshisue K, Matsushima E et al. Bioactivation of tegafur to 5-fluorouracil is catalyzed by cytochrome P-450 2A6 in human liver microsomes in vitro. Clin Cancer Res 2000; 6: 4409–4415.
23. Ajani JA, Faust J, Ikeda K et al. Phase I pharmacokinetic study of S-1 plus cisplatin in patients with advanced gastric carcinoma. J Clin Oncol 2005; 23: 6957–6965.