Postoperative adjuvant chemotherapy regimen of capox combined with ninjin'yoeito ...

Health & Medicine

Introduction

Combinations of oxaliplatin (L-OHP) with fluoropyrimidine drugs have been used as standard adjuvant chemotherapy regimens for the treatment of stage III colon cancer since 2004. Although elderly patients reap the same benefits from these regimens as younger patients, the main adverse effect of L-OHP is peripheral neuropathy. In previous reports, ninjin'yoeito (NYT) was reported to be useful for reducing adverse effects such as anticancer anemia, peripheral neuropathy, and cancer cachexia (1 – 4). We report a case of postoperative adjuvant chemotherapy comprising capecitabine plus L-OHP (CAPOX) combined with NYT for the treatment of stage III colon cancer in an elderly patient.

Case Presentation

A 75-year-old woman with a medical history of hypertension presented at another institution with fecal occult blood, and a colonoscopy showed a type II tumor in the sigmoid colon. She was referred to our hospital for tumor resection, where colonoscopy determined that the tumor was located 23 cm from the anal verge. Histopathology of a biopsy specimen revealed a moderately differentiated tubular adenocarcinoma. Enhanced computed tomography of the thorax and abdomen showed sigmoid colon wall thickening. Regional lymph node metastasis was suspected, but no evidence of distant metastasis was observed. A blood examination revealed an elevated carcinoembryonic antigen (CEA) concentration (32. 7 ng/ml). Following a diagnosis of cancer of the sigmoid colon, clinical stage IIIb [cT4a, N1b, M0], a laparoscopic sigmoid colectomy was performed without

complications. The postoperative histopathological examination revealed a moderately differentiated to mucinous adenocarcinoma. Three of the 16 retrieved lymph nodes contained malignant cells. Finally, the cancer was classified as stage IIIb [pT4a, pN1b, M0]. The patient recovered uneventfully and was discharged 10 days after the surgery. Following the diagnosis of stage III colorectal cancer, the patient was recommended to receive adjuvant chemotherapy with CAPOX starting 4 weeks after surgery. The selected regimen consisted of capecitabine (1, 000 mg/m ^{2} orally twice daily) for 14 days and L-OHP (130 mg/m ^{2} intravenous infusion) on the first day of each cycle, with a periodicity of 3 weeks over 3 months (four cycles). The anticancer drug dosage was reduced to 80% because of the patient's age. The patient had postoperative physical weakness and appetite loss, and also received 7. 5 g of NYT daily throughout the course of adjuvant chemotherapy. She did not report any events of peripheral loss of appetite, general fatigue, peripheral neuropathy, neutropenia, or febrile neutropenia. Adverse effects were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v5. 0. She has not experienced any recurrence during a 1-year postoperative follow-up.

Discussion

Herein, we report the successful management of stage III colon cancer in an elderly patient via adjuvant CAPOX chemotherapy combined with NYT. Adjuvant chemotherapy improves overall survival in patients with resected stage III colorectal cancer (5). The MOSAIC Multicenter International Study (6) revealed that a regimen of FOLFOX [fluorouracil (FU) bolus and

continuous infusion combined with leucovorin (LV) and L-OHP] significantly improved 3-year disease-free survival outcomes when compared with fluorouracil and leucovorin alone. Additionally, CAPOX improved overall survival outcomes in patients with resected stage III colon cancer when compared with bolus FU after a median follow-up of almost 7 years (7). CAPOX allows for central venous (CV)-port-free administration. Therefore, this regimen might be considered a standard adjuvant treatment option for patients with stage III colon cancer.

Elderly patients receive the same survival benefit from these regimens as younger patients. In both older (≥70 years) and younger patients, adjuvant 5-FU therapy has been significantly associated with reduced mortality in randomized controlled trials (8). Haller reported that in a pooled analysis of individual patient data from four randomized controlled trials of CAPOX/FOLFOX vs. LV/5-FU [NSABP C-08 (9), XELOXA (7), X-ACT (10), and AVANT (11)], disease-free survival benefits were observed regardless of age or medical comorbidity. However, the benefits were modestly attenuated in patients aged ≥70 years, with a hazard ratio of 0. 77 ($P < 0.$ 014) vs. 0. 68 ($P < 0.$ 0001) among patients aged <70 years (12).

Peripheral neuropathy is the main adverse effect of L-OHP therapy. In the MOSAIC study, grade 2 and 3 peripheral sensory neuropathy was observed during treatment in 31. 4 and 12. 5% patients in the FOLFOX group (13). During treatment with L-OHP chemotherapy, patients have experienced acute and chronic mechanical hyperalgesia and cold allodynia. The dose and duration of therapy are limited once a patient develops peripheral

neuropathy, leading to a reduced quality of life. The cumulative administered dose of L-OHP increases the risk of associated sensory neurotoxicity (13 , 14). In the MOSAIC trial (13), the frequency of grade 3 peripheral sensory neuropathy among patients receiving L-OHP persisted over time (1. 3% at 12 months and 0. 7% at 48 months after treatment). This toxic adverse effect may be severe and can persist long after treatment is completed, leading to potentially life-long effects on the patients' activities of daily living (15).

To date, various integrative approaches, including Japanese kampo medicine, have been used in an attempt to prevent the adverse effects of chemotherapy. Kampo medicines are currently used to treat several types of diseases, and are also used to improve the quality of life of patients throughout the world and especially in Asian countries (3). Of the traditional medicine components prescribed to prevent L-OHP-induced peripheral neuropathy, goshajinkigan has been the most popular with animal experiments (16 – 18). However, goshajinkigan could not prevent L-OHP-induced peripheral neurotoxicity in colorectal cancer patients treated with FOLFOX regimens in a randomized phase III clinical trial (19).

NYT is a Japanese kampo medicine composed of 12 herbal plants that is used to facilitate disease recovery and improve several symptoms, such as anemia, anorexia, and fatigue. In previous reports, NYT appeared to be useful for reducing the adverse effects of anticancer anemia, peripheral neuropathy and cancer cachexia (1 – 4). NYT should be administered at the same time as adjuvant chemotherapy. At that time, the indicating disease, such as postoperative physical weakness, general fatigue, appetite loss, and

anemia, must be present. Some references indicate that more human data, both younger and elderly patients, is needed to validate the efficacy of NYT in managing adverse effects of a systemic chemotherapy regimen (20 , 21). In mice, NYT improved 5-FU-induced anemia and increased the populations of burst-forming unit-erythroid cells and colony-forming unit-erythroid cells in bone marrow (22).

In an *in vitro* study, Suzuki reported that an extract of NYT prevented L-OHP-induced neurodegeneration in PC12 cells (1). Particularly, ginseng extract appeared to exert the strongest protective effect against neurodegeneration among the 12 herbal components of NYT. In a mouse model experiment, NYT and ginseng reduced L-OHP-induced neurite damage and neuropathic pain. In an *in vitro* study, L-OHP treatment suppressed neurite outgrowths from primary dorsal root ganglion cells. NYT extract blocked this suppression in a concentration-dependent manner. Ginseng showed a protective effect against neurite damage induced by L-OHP, and one of its active ingredients was identified as ginsenoside Rg3 (4). In addition to NYT, other kampo medicines, such as ginseng and hochuekkito also reduce the adverse effects of anticancer therapy. Hochuekkito is not expected to improve peripheral neuropathy, but has been noted to improve gastrointestinal conditions and increase physical strength, and is expected to improve immune function (23). Consistent with those earlier observations, the administration of NYT reduced the adverse effects associated with adjuvant CAPOX chemotherapy, such as peripheral neuropathy, neutropenia, and febrile neutropenia in our elderly patient with stage III colorectal cancer.

In conclusion, our observations suggest that NYT might be useful for reducing the adverse effects of anticancer therapy in elderly patients.

Data Availability Statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation, to any qualified researcher.

Ethics Statement

The studies involving human participants were reviewed and approved by Ethical Committee of the Fuchu Hospital. The patients/participants provided their written informed consent to participate in this study.

Author Contributions

NA made a substantial contribution to the study conception, conducted a literature search, and drafted the manuscript. NA and GT contributed to the acquisition of data. NA, SK, TO, and YU performed the surgery. NA, YU, GT, YM, TO, SK, SM, TH, TI, JM, SY, KN, TN, AT, KM, KI, and KT reviewed the manuscript and gave final approval for publication. All authors read and approved the final manuscript.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

1. Suzuki T, Yamamoto A, Ohsawa M, Motoo Y, Mizukami H, Makino T. Ninjin'yoeito and ginseng extract prevent oxaliplatin-induced neurodegeneration in PC12 cells. *J Nat Med.* (2015) 69: 531–7. doi: 10. 1007/s11418-015-0921-9

PubMed Abstract | CrossRef Full Text | Google Scholar

2. Ohsawa M, Maruoka J, Inami C, Iwaki A, Murakami T, Ishikura K. Effect of ninjin'yoeito on the loss of skeletal muscle function in cancer-bearing mice. *Front Pharmacol.* (2018) 9: 1400. doi: 10. 3389/fphar. 2018. 01400

PubMed Abstract | CrossRef Full Text | Google Scholar

3. Miyano K, Nonaka M, Uzu M, Ohshima K, Uezono Y. Multifunctional actions of Ninjinyoeito, a Japanese kampo medicine: accumulated scientific evidence based on experiments with cells and animal models, and clinical studies. *Front Nutr* . (2018) 5: 93. doi: 10. 3389/fnut. 2018. 00093

PubMed Abstract | CrossRef Full Text | Google Scholar

4. Suzuki T, Yamamoto A, Ohsawa M, Motoo Y, Mizukami H, Makino T. Effect of ninjin'yoeito and ginseng extracts on oxaliplatin-induced neuropathies in mice. *J Nat Med.* (2017) 71: 757–64. doi: 10. 1007/s11418-017-1113-6

PubMed Abstract | CrossRef Full Text | Google Scholar

5. Moertel CG, Fleming TR, Macdonald JS, Haller DG, Laurie JA, Goodman PJ, et al. Levamisole and fluorouracil for adjuvant therapy of resected colon

carcinoma. *N Engl J Med.* (1990) 322: 352–8. doi: 10. 1056/NEJM199002083220602

PubMed Abstract | CrossRef Full Text | Google Scholar

6. Andre T, Boni C, Mounedji-Boudiaf L, Navarro M, Tabernero J, Hickish T, et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. *N Engl J Med.* (2004) 350: 2343–51. doi: 10. 1056/NEJMoa032709

PubMed Abstract | CrossRef Full Text | Google Scholar

7. Schmoll HJ, Tabernero J, Maroun J, de Braud F, Price T, Van Cutsem E, et al. Capecitabine plus oxaliplatin compared with fluorouracil/folinic acid as adjuvant therapy for stage iii colon cancer: final results of the NO16968 Randomized Controlled Phase III Trial. *J Clin Oncol.* (2015) 33: 3733–40. doi: 10. 1200/JCO. 2015. 60. 9107

PubMed Abstract | CrossRef Full Text | Google Scholar

8. Sundararajan V, Mitra N, Jacobson JS, Grann VR, Heitjan DF, Neugut AI. Survival associated with 5-fluorouracil-based adjuvant chemotherapy among elderly patients with node-positive colon cancer. *Ann Intern Med* . (2002) 136: 349–57. doi: 10. 7326/0003-4819-136-5-200203050-00007

PubMed Abstract | CrossRef Full Text | Google Scholar

9. Allegra CJ, Yothers G, O'Connell MJ, Sharif S, Petrelli NJ, Colangelo LH, et al. Phase III trial assessing bevacizumab in stages II and III carcinoma of the

colon: results of NSABP protocol C-08. *J Clin Oncol.* (2011) 29: 11–6. doi: 10. 1200/JCO. 2010. 30. 0855

PubMed Abstract | CrossRef Full Text | Google Scholar

10. Twelves C, Wong A, Nowacki MP, Abt M, Burris H 3rd, Carrato A, et al. Capecitabine as adjuvant treatment for stage III colon cancer. *N Engl J Med.* (2005) 352: 2696–704. doi: 10. 1056/NEJMoa043116

PubMed Abstract | CrossRef Full Text | Google Scholar

11. de Gramont A, Van Cutsem E, Schmoll HJ, Tabernero J, Clarke S, Moore MJ, et al. Bevacizumab plus oxaliplatin-based chemotherapy as adjuvant treatment for colon cancer (AVANT): a phase 3 randomised controlled trial. *Lancet Oncol.* (2012) 13: 1225–33. doi: 10. 1016/S1470-2045(12)70509-0

PubMed Abstract | CrossRef Full Text | Google Scholar

12. Haller DG, O'Connell MJ, Cartwright TH, Twelves CJ, McKenna EF, Sun W, et al. (2015). Impact of age and medical comorbidity on adjuvant treatment outcomes for stage III colon cancer: a pooled analysis of individual patient data from four randomized, controlled trials. *Ann Oncol* . (2015) 26: 715–24. doi: 10. 1093/annonc/mdv003

PubMed Abstract | CrossRef Full Text | Google Scholar

13. Grothey A, Sobrero AF, Shields AF, Yoshino T, Paul J, Taieb J, et al. Duration of adjuvant chemotherapy for stage iii colon cancer. *N Engl J Med.* (2018) 378: 1177–88. doi: 10. 1056/NEJMoa1713709

PubMed Abstract | CrossRef Full Text | Google Scholar

14. Andre T, Boni C, Navarro M, Tabernero J, Hickish T, Topham C, et al. Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. *J Clin Oncol.* (2009) 27: 3109–16. doi: 10. 1200/JCO. 2008. 20. 6771

CrossRef Full Text | Google Scholar

15. Grothey A. Oxaliplatin-safety profile: neurotoxicity. *Semin Oncol.* (2003) 30: 5–13. doi: 10. 1016/S0093-7754(03)00399-3

PubMed Abstract | CrossRef Full Text | Google Scholar

16. Ushio S, Egashira N, Sada H, Kawashiri T, Shirahama M, Masuguchi K, et al. Goshajinkigan reduces oxaliplatin-induced peripheral neuropathy without affecting anti-tumour efficacy in rodents. *Eur J. Cancer.* (2012) 48: 1407–13. doi: 10. 1016/j. ejca. 2011. 08. 009

PubMed Abstract | CrossRef Full Text | Google Scholar

17. Kitamura R, Andoh T, Fushimi H, Komatsu K, Shibahara N, Kuraishi Y. Involvement of descending monoaminergic systems in antiallodynic effect of goshajinkigan in oxaliplatin-treated mice. *J Trad Med.* (2013) 30: 183–9.

Google Scholar

18. Mizuno K, Kono T, Suzuki Y, Miyagi C, Omiya Y, Miyano K, et al. Goshajinkigan, a traditional Japanese medicine, prevents oxaliplatin-induced

acute peripheral neuropathy by suppressing functional alteration of TRP channels in rat. *J Pharmacol Sci* . (2014) 13244FP. doi: 10. 1254/jphs. 13244FP

PubMed Abstract | CrossRef Full Text | Google Scholar

19. Oki E, Emi Y, Kojima H, Higashijima J, Kato T, Miyake Y, et al. Preventive effect of Goshajinkigan on peripheral neurotoxicity of FOLFOX therapy (GENIUS trial): a placebo-controlled, double-blind, randomized phase III study. *Int J Clin Oncol* . (2015) 20: 767–75. doi: 10. 1007/s10147-015-0784-9

PubMed Abstract | CrossRef Full Text | Google Scholar

20. Sugimachi K. Igan Jutsugo hozyokagakuryouhou ni okeru Ninjin'yoeito no yuuyouseini kannsuru kennkyuu (Study of efficacy of Ninjin Yoei-to for adjuvant chemotherapy after gastric cancer surgery). *Jpn J Clin Exp Med* . (1995) 72: 454–8.

Google Scholar

21. Abe K. Jutsugo hojokagakuryouhou ni okeru Ninjin Yoei-to no yuuyousei ni kannsurukennkyuu (Experience of use of Ninjin Yoei-to in postoperative maintenance chemotherapy). *Progress Med* . (1990) 10: 2855–63.

Google Scholar

22. Takano F, Ohta Y, Tanaka T, Sasaki K, Kobayashi K, Takahashi T, et al. Oral administration of Ren-shen-yang-rong-tang 'ninjin'yoeito'protects against hematotoxicity and induces immature erythroid progenitor cells in 5-

fluorouracil-induced anemia. *Evid Based Complement Alternat Med.* (2009) 6: 247–56. doi: 10. 1093/ecam/nem080

PubMed Abstract | CrossRef Full Text | Google Scholar

23. Kono T, Takeda H, Uezono Y. Kampo medicine for the treatment of adverse effects caused by anticancer drugs. *Nihon Geka Gakkai Zasshi.* (2013) 114: 251–5.

PubMed Abstract | Google Scholar