A Case of Advanced Esophageal Cancer Showing a Long-term Complete Response with Chemotherapy with Nedaplatin Alone

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We describe a case of advanced esophageal cancer treated successfully by chemotherapy with nedaplatin alone. A 60-year-old male with type 2 advanced esophageal cancer, which was located in the upper part of the esophagus and had invaded adjacent organs, was treated with nedaplatin 150 mg/body (100 mg/m²) given intravenously every 4 weeks from January 6, 1991. He achieved a partial response (PR) and was discharged in March 1991. Subsequently, he received nedaplatin 75 mg/body in an out-patient setting almost every month until August 1992. Toxicities were tolerable and included mild thrombocytopenia and nausea/vomiting. From serial evaluation in October 1993, the esophageal tumor was not observed. After 7 years since initial chemotherapy was administered, he still survives without the disease.

Key words: nedaplatin – esophageal cancer

INTRODUCTION

With the development of combination chemotherapy containing cisplatin, clinical results of esophageal cancer have become relatively more favorable than those for other gastrointestinal cancers. However, cases with advanced esophageal cancer who respond to chemotherapy and achieve complete response (CR) with long-term survival are still rare. We report a patient with advanced esophageal cancer who was treated with nedaplatin 254-S (cis-diammineglycolatoplatinum) alone and achieved CR and has maintained long-term survival.

CASE REPORT

In December 1990, a 60-year-old male was seen in the Otorhinolaryngology Department of our hospital because of dysphasia, difficulty in eating solid food, backache and weight loss of 2 kg over the previous 2 months. His past medical history included operated cholecystitis in 1972, pancreatitis in 1976 and percutaneous transluminal coronary angioplasty in 1989 due to angina pectoris. A barium esophagogram showed abnormal findings in his thoracic esophagus. He was referred and admitted to our department for further examination and therapy.

On admission, no abnormal findings were found on physical examination. Laboratory studies including peripheral blood, biochemistry and tumor markers showed no abnormal values. The barium-filled esophagogram showed an irregular ragged mucosal pattern with luminal narrowing of 7.5 cm length in the upper part of the thoracic esophagus (Fig. 1). Endoscopic examination revealed a deep excavative lesion with an irregular surface, which was diagnosed as a type 2 advanced esophageal cancer (Fig. 2). Several biopsy specimens were taken from the ulcerated and non-ulcerated areas of the esophageal tumor. The histological diagnosis was poorly differentiated squamous cell carcinoma (Fig. 3). A chest computed tomographic scan demonstrated that the tumor had invaded the thoracic aorta and the trachea (Fig. 4). This case was diagnosed as stage III disease by TNM classification and was not considered feasible for operation owing to tumor invasion to adjacent organs and possible impairment of cardiac function. He was informed about a phase II clinical study with 254-S and preferred to receive nedaplatin instead of other therapies such as 5-FU plus cisplatin, because administration of 5-FU and the vigorous hydration needed for cisplatin might affect his cardiac function.

A chemotherapy regimen of nedaplatin 150 mg/body (100 mg/m²) given intravenously was performed every 4 weeks from...
Figure 1. (a) The barium-filled esophagogram showed an irregular ragged mucosal pattern with luminal narrowing of 7.5 cm diameter in the upper of the thoracic esophagus on admission in December 1990. (b) A repeat esophagogram after therapy did not reveal any macroscopic evidence of tumor in October, 1993.

Figure 2. (a) The endoscopic examination revealed a deep excavative lesion with an irregular surface, which was diagnosed as a type 2 advanced esophageal cancer on admission in December 1990. (b) In a repeat endoscopy after treatment the tumor was not recognized at all and there was no unstained area on iodine staining in March 1998.

January 6, 1991. Two weeks after the first cycle of chemotherapy, the patient showed a marked improvement in his dysphagia. A repeated barium esophagogram after the third cycle revealed a reduction more than 80% of the esophageal tumor. He was considered to have achieved a partial response (PR) and we permitted discharge in March 1991 for his quality of life. A formal protocol study was completed at the time of the discharge. When considering maintenance therapy, however, the drug which was expected to show a definite effect in an out-patient setting was limited. In this case, nedaplatin has been already found to be effective and safely given without unfavorable symptoms in
Several cytotoxic drugs such as CDDP, bleomycin, mytomycin C, vindesine, methotrexate and 5-fluorouracil have shown anti-tumor activity against esophageal cancer, with response rates of over 20% in monotherapy. Combinations of these drugs have provided response rates of 50–60%, most of them limited to partial response and did not improve survival (1). CDDP is one of the most active agents for esophageal cancer, with a single-agent response rate of 32.4% in a phase II clinical study of SWOG (2). It has been used in various combination chemotherapies as a key drug. However, its toxicities, including nephrotoxicity and gastrointestinal toxicity, may require frequent modifications of treatment. Several platinum complexes have been synthesized and screened in an attempt to develop drugs with antitumor activity equal to or greater than and toxicities lower than those of CDDP. Nedaplatin is a second-generation platinum complex that was developed by Shionogi Pharmaceutical Company (Osaka, Japan). It combines with DNA in a similar fashion to CDDP and interferes with duplication of DNA. Compared with CDDP, preclinical studies have demonstrated that nedaplatin has higher anti-tumor activity with both lower renal toxicity and higher aqueous solubility (3). In a phase I clinical study, no significant nephrotoxicity was found, although bone marrow suppression (thrombocytopenia and leukopenia) was regarded as a major dose-limiting factor. The recommended dose and schedule for a phase II study were determined to be 100 mg/m² given at intervals of 4 weeks (4, 5). Nedaplatin showed a high response rate of 51.7% for esophageal cancers in a phase II study (6). We have experienced five PR cases out of nine patients with advanced esophageal cancer who were treated with 254-S (7). In contrast to CDDP, nedaplatin does not require vigorous hydration, which suggests the utility of this agent in ambulatory treatment. In this study, nedaplatin was given by monotherapy against advanced esophageal cancer and yielded a complete response which is still ongoing. This indicates the potential of nedaplatin in the chemotherapy of esophageal cancer.

In conclusion, the presented case suggests that nedaplatin is a promising agent for the chemotherapy of esophageal cancer as a key drug and might be a substitute for CDDP.

### DISCUSSION

Several cytotoxic drugs such as CDDP, bleomycin, mytomycin C, vindesine, methotrexate and 5-fluorouracil have shown anti-tumor activity against esophageal cancer, with response rates of over 20% in monotherapy. Combinations of these drugs have provided response rates of 50–60%, most of them limited to partial response and did not improve survival (1). CDDP is one of the most active agents for esophageal cancer, with a single-agent response rate of 32.4% in a phase II clinical study of SWOG (2). It has been used in various combination chemotherapies as a key drug. However, its toxicities, including nephrotoxicity and gastrointestinal toxicity, may require frequent modifications of treatment. Several platinum complexes have been synthesized and screened in an attempt to develop drugs with antitumor activity equal to or greater than and toxicities lower than those of CDDP. Nedaplatin is a second-generation platinum complex that was developed by Shionogi Pharmaceutical Company (Osaka, Japan). It combines with DNA in a similar fashion to CDDP and interferes with duplication of DNA. Compared with CDDP, preclinical studies have demonstrated that nedaplatin has higher anti-tumor activity with both lower renal toxicity and higher aqueous solubility (3). In a phase I clinical study, no significant nephrotoxicity was found, although bone marrow suppression (thrombocytopenia and leukopenia) was regarded as a major dose-limiting factor. The recommended dose and schedule for a phase II study were determined to be 100 mg/m² given at intervals of 4 weeks (4, 5). Nedaplatin showed a high response rate of 51.7% for esophageal cancers in a phase II study (6). We have experienced five PR cases out of nine patients with advanced esophageal cancer who were treated with 254-S (7). In contrast to CDDP, nedaplatin does not require vigorous hydration, which suggests the utility of this agent in ambulatory treatment. In this study, nedaplatin was given by monotherapy against advanced esophageal cancer and yielded a complete response which is still ongoing. This indicates the potential of nedaplatin in the chemotherapy of esophageal cancer.

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### References