Complete Remission of Mediastinal Germ-Cell Tumors With cis-Dichlorodiammineplatinum(II) Combination Chemotherapy

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SUMMARY

Two patients with mediastinal germ-cell tumors achieved a complete remission with the combination of vinblastine, bleomycin, and cis-dichlorodiammineplatinum(II).


The occurrence of germ-cell tumors in the mediastinum is well-known and has given rise to speculation about their origin. The question is whether these neoplasms arise as primary tumors in localizations other than the testes.

Because fibrous scars (1,2) and microscopic tumor foci (3) are found in the testes of patients with extensive extratesticular neoplasms at autopsy, the clinician must decide whether a mediastinal tumor with histologic features of testicular carcinoma is a primary or a metastatic lesion. Utz and Buscemi (4) consider this neoplasm to be a primary tumor if the testes are normal on palpation. The absence of retroperitoneal disease may provide support for this conclusion.

The prognosis of mediastinal tumors is not determined solely by the response to chemotherapy. Patients may die shortly after presentation due to invasion or compression of vital organs. Treatment results in patients with seminomas are good, whereas results obtained in patients with mediastinal teratocarcinoma, choriocarcinoma, and embryonal carcinoma have been disappointing, with survival times of < 6 months (2,5,6).

In connection with this problem, the two patients referred to our Department of Internal Medicine for chemotherapy for a mediastinal germ-cell tumor during the past 2 years were treated with chemotherapy alone. Both patients, one with embryonal carcinoma and the other with seminoma, obtained a complete remission with the combination of vinblastine, bleomycin, and cis-dichlorodiammineplatinum(II) (CDDP).

CASE REPORTS

Patient 1

Patient 1, a 24-year-old student, gradually developed complaints of tiredness and dyspnea (June 1977). Physical examination revealed dullness of the left hemithorax and a puncture produced hemorrhagic fluid. Thoracotomy showed a tumor arising from the anterior mediastinum and filling the left hemithorax. The histologic diagnosis was embryonal carcinoma locally differentiating towards a yolk sac (endodermal sinus) tumor. The testes were normal on palpation. A lymphangiogram showed normal nodes. The LDH was elevated to 600 units/liter. The α-fetoprotein level was reported to be between 200 and 1000 ng/ml. The β-human chorionic gonadotropin was negative. Polychemotherapy consisting of CDDP (20 mg/m² for 5 days), vinblastine (0.2 mg/kg of body weight on Days 1 and 2), and bleomycin (30 mg/kg/week) was started. The courses were repeated every 3 weeks, and a total of four courses were given. After the fourth course the tumor seemed smaller. The α-fetoprotein level was 4 ng/ml. In October 1977, a percutaneous puncture produced necrotic material. Thoracotomy showed a large solid tumor arising from the anterior mediastinum and adhering to the pericardium, pulmonary vessels, left main bronchus, and left upper lobe. The mass and the left lung were removed entirely. Histologic examination showed only necrotic tumor tissue. Maintenance therapy consisting of vinblastine (0.2 mg/kg of body weight every 3 weeks) and CDDP (30 mg/m² [reduced dose because of diminished creatinine clearance]) every 6 weeks was started in November 1977. A complete remission has lasted at least since October 1977 (and probably longer), and the patient is now successfully studying dentistry.

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Patient 2

Patient 2, a 19-year-old student, was found to have a mediastinal mass during a medical examination for military service in 1974. Histologic examination of the material removed at thoracotomy revealed a seminoma. The tests were normal on palpation. Retroperitoneal exploration was not performed. Postoperatively, the mass was irradiated with a dose of 4000 rads and subsequently disappeared. The retroperitoneal lymph nodes were not irradiated. In August 1975, the patient complained of back pain. A roentgenogram showed a metastasis to the left 11th rib, which was confirmed cytologically. LDH activity was 1300 units/liter. Radiotherapy induced a remission which lasted 5 months.

In January 1976, supraclavicular masses were found on both sides. Histologic examination revealed metastasis of seminoma. Mechlorethamine was started at a dose of 0.1 mg/kg of body weight for 4 days followed by a dose of 0.1 mg/kg every 3 weeks, and remission was again achieved.

In February 1977, his condition worsened. Physical examination showed a superior caval vein syndrome and a mass in the left supraclavicular fossa; the hepatic extended 6 cm below the right arcus costae. The lumbar vertebræ were normal. After additional radiotherapy (1500 rads) was applied to the mediastinum, right hilus, and left supraclavicular fossa, the masses disappeared and the superior caval vein syndrome subsided. The chemotherapy was continued in two courses which included actinomycin D (0.5 mg iv for 5 days), vincristine (1 mg on Days 1 and 5), and chlorambucil (8 mg for 14 days).

In June 1977, the patient again complained of back pain. Physical examination showed a radicular syndrome and fractures of the first and second lumbar vertebrae. After radiotherapy (3000 rads), all symptoms disappeared. The patient refused further treatment and had followup until January 1978 when he gradually became dyspneic. Physical examination showed a firm tumor on the left thoracic wall. Cytologic investigation showed an undifferentiated tumor. A roentgenogram showed a mass in the mediastinum, atelectasis of the left lower lobe, and a mass in the right hilus.

In February 1978, the patient was referred to our department for chemotherapy. We decided to give him a course of vinblastine (0.1 mg/kg of body weight on Days 1 and 2) and CDDP (20 mg/m² for 5 days) to be repeated every 3 weeks. The initial two courses were given without bleomycin because of the possibility of pulmonary fibrosis caused by heavy previous radiation therapy. The LDH activity before the first course was 1500 units/liter; after the second course, the level returned to normal (188 units/liter). The masses disappeared. A complete remission was achieved after the second course and has lasted 26 months. The α-fetoprotein and β-human chorionic gonadotropin subunit have never been elevated. Four courses were given; the third and fourth courses included bleomycin at a weekly dose of 30 mg. Each course resulted in leukopenia and thrombocytopenia, but no septic or hemorrhagic complications occurred. Maintenance therapy, consisting of vinblastine (0.1 mg/kg of body weight every 3 weeks) and CDDP (50 mg/m² every 6 weeks) was continued until June 1979. At present, the patient is successfully studying law.

DISCUSSION

In these two patients, the combination of vinblastine, bleomycin, and CDDP induced complete remissions of 32 and 26 months.

The non-seminomatous germ-cell tumors are known to be relatively resistant to therapy (7). After Li et al (8) and Samuels et al (6), Einhorn and Donohue (9,10) achieved major progress in the treatment of non-seminomatous testicular carcinoma.

Surgery has been the first step in the treatment of mediastinal non-seminomatous carcinoma, and was performed where the histologic diagnosis was still unknown. Radiation therapy has not appreciably prolonged survival (2,7). In some patients, however, multiple-drug therapy has been used successfully, with survival times of 30 and 68 months (11). Our first patient had an inoperable tumor diagnosed as embryonal carcinoma. We decided to treat him identically to our patients with testicular germ-cell carcinoma. Because we had frequently found necrotic and fibrotic tumor tissue at retroperitoneal lymph-node dissection after remission induction, we performed a thoracotomy to explore the residual mass and found only necrotic tumor tissue.

Radiotherapy is the treatment of choice for pure testicular seminoma. Reported cure rates reach 95% (5). In this respect, mediastinal seminomas do not seem to differ from the testicular seminomas.

A review of Besznyák et al (12) on mediastinal seminoma indicates a 1-year survival rate of 90% after combined surgical treatment and radiation therapy. Seventeen of 18 patients who were given only radiotherapy lived > 1 year. The favorable influence of radiotherapy has been confirmed by other investigators (7,13–15). The high response rate to radiation therapy permits low doses, so that the heart and lungs are at low-risk with respect to radiation therapy effects. We recommend radiotherapy for mediastinal seminoma after surgery, which is usually required for diagnostic purposes. Radiotherapy for metastatic lesions of testicular seminoma results in a 5-year survival rate of 55% (16). For advanced cases, chemotherapy is the treatment of choice. Alkylating agents are said to give the best results (17,18). Recently, complete remissions obtained with the combination of vinblastine, bleomycin, and CDDP have been reported (9,10). Over
the last 3 years "therapy-resistant" testicular seminoma has been treated like non-seminomatous testicular neoplasms with this drug combination giving excellent results (19). On this basis and the excellent results obtained in patient 2, we propose the use of this drug combination whenever chemotherapy is indicated for widespread metastases of seminoma.

In our opinion, the best way to treat non-seminomatous germ-cell tumors of the mediastinum is by using the combination of vinblastine, bleomycin, and CDDP, thus avoiding high-dose radiotherapy with its harmful effects on the heart and lung, its detrimental effects on the bone marrow reserves, and its high risk of pulmonary fibrosis in conjunction with bleomycin. A recent review describes 19 patients treated with several vinblastine, actinomycin D, and bleomycin protocols resulting in two complete remissions and eight partial remissions, with an overall objective response rate of 53% (20). However, because the incidence of mediastinal germ-cell tumors is so low, it will not be possible to collect sufficiently large series to determine whether it is indeed correct to base the treatment of this kind of neoplasm on the histologic resemblance to testicular carcinoma.

REFERENCES