Salvage Therapy in Patients with Germ Cell Tumors

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OVERVIEW

Testicular cancer is the most curable metastatic solid tumor. Initial chemotherapy is evidence based with risk stratification into three prognostic categories: good, intermediate, and advanced disease. Guidelines for disease management following progression after initial cisplatin combination chemotherapy are less clear. Options include salvage surgery for patients with anatomically confined relapse, standard-dose cisplatin combination chemotherapy, or high-dose chemotherapy with carboplatin plus etoposide with peripheral blood stem cell transplantation. Proper interpretation of a presumed relapse can be complicated. Growing masses on imaging studies might reflect a growing teratoma. Persistent elevations of serum human chorionic gonadotropin (hCG) or alpha fetoprotein (AFP) are only an indication for salvage therapy if there is a definitive rise in the tumor marker. Elevated and rising serum hCG as the only evidence of recurrence can be because of cross reactivity with luteinizing hormone or usage of marijuana rather than progressive cancer. Elevated liver function tests can cause rising serum AFP.

The initiation of cisplatin combination chemotherapy 40 years ago transformed metastatic testicular cancer into a highly curable malignancy. It is widely recognized to be the most curable solid tumor. Subsequent salvage strategies have allowed for cure in a substantial percentage of progressive disease following first-line cisplatin combination chemotherapy. This article will detail strategies for salvage chemotherapy, the judicious use of salvage surgery, and data from published studies.

The first curative salvage chemotherapy utilized the two-drug synergistic combination of cisplatin plus etoposide in patients in which cisplatin plus vinblastine plus bleomycin failed. Our strategy at the inception of this phase II study, initiated in 1978, is still appropriate today, namely the continued use of cisplatin unless a patient’s disease progressed within 4 weeks from his prior regimen (platinum refractory) and the incorporation of other active agent(s) not previously utilized. In this early study, we achieved a 25% cure rate, demonstrating the synergism of this two-drug combination. Neither single-agent cisplatin nor etoposide would be expected to have any realistic prospect for cure as second-line chemotherapy. Subsequently, etoposide replaced vinblastine as first-line chemotherapy. Subsequent standard-dose salvage regimens for patients who did not have platinum refractory disease consisted of either vinblastine plus ifosfamide plus cisplatin or paclitaxel plus ifosfamide plus cisplatin (TIP). Today either of these standard-dose salvage chemotherapy programs are appropriate as second-line chemotherapy.

The era of successful high-dose chemotherapy with bone marrow or peripheral blood stem cell transplant began in 1986 with the introduction of carboplatin. The philosophy of autologous stem cell transplant is to utilize high doses of cytolytic agents that are active for that particular malignancy and for which major dose-limiting toxicity can be rescued by the stem cell transplant, namely myelosuppression. This has largely been a failed strategy in other solid tumors such as melanoma and breast cancer. We began studies with high-dose carboplatin and etoposide in 1986 with bone marrow transplants, and subsequently with peripheral blood stem cell transplants in 1996. The latter study enrolled 184 consecutive patients, of whom 116 of 184 (63%) are continuously disease free, including 22 of 49 (45%) who received treatment as third-line therapy, and 18 of 40 (45%) who were deemed to have platinum refractory disease. This study demonstrated the ability of high-dose platinum plus etoposide to overcome drug resistance from standard doses of cisplatin and etoposide.

Memorial Sloan Kettering Cancer Center has pioneered an innovative approach with three courses of high-dose carboplatin plus etoposide (compared with the tandem transplant at Indiana University) albeit at somewhat lower doses. This regimen is preceded by paclitaxel and ifosfamide (TI-CE). There are no randomized studies suggesting any specific strategy of high-dose chemotherapy is preferred. There does not appear to be optimal benefit when only one course of high-dose chemotherapy is used. Likewise, there is indirect evidence that adding a third drug to carboplatin plus etoposide is not beneficial.

There also have been no randomized phase III studies suggesting or proving superiority of one form of standard-dose salvage chemotherapy. Likewise, there is no evidence-based medicine demonstrating that initial salvage chemotherapy should be high-dose versus standard-dose chemotherapy. A retrospective international analysis was performed by Lorch et al that categorized salvage chemotherapy patients into five prognostic subtypes. In a retrospective analysis, the same group of
investigators compared standard-dose with high-dose chemotherapy as initial salvage chemotherapy in 1,594 patients. Seven hundred and seventy-three patients received a standard dose and 821 received high-dose chemotherapy with 2-year progression-free survival being 27.8% versus 49.6% and 5-year survival being 40.8% versus 53.2%. High-dose chemotherapy is the preferred option for patients with platinum refractory disease or for patients with disease progressing after standard-dose salvage chemotherapy. However, there are no prospective randomized studies proving superiority of high-dose chemotherapy. An argument can also be made that there are no phase III trials proving the merit of standard-dose cisplatin plus ifosfamide combination chemotherapy. A randomized trial comparing TIP versus TI-CE is on the drawing board for initial salvage chemotherapy. If this trial can be completed, it would answer the question comparing these two regimens.

Testis cancer is clearly a remarkably chemosensitive and chemocurative tumor. However, it is also the most curable cancer with surgery alone as initial therapy for node-positive disease. Salvage surgery is the preferred option for initial salvage therapy if progression is anatomically confined and surgically resectable.

ADDITIONAL SALVAGE THERAPIES

It is very difficult, if not impossible, to cure disease with further standard-dose platinum-based chemotherapy after high-dose chemotherapy fails. Approximately 10% of such patients will experience a 5-year disease-free survival with weekly paclitaxel plus gemcitabine, assuming they have not received prior paclitaxel therapy such as TIP. Modest success has also been achieved with gemcitabine plus oxaliplatin or adding paclitaxel plus gemcitabine plus oxaliplatin. There remains a cohort of patients in which their disease is not cured. Feldman et al evaluated 97 such patients treated with various single agents. There was only one patient partial remission and 15 patients with stable disease. Daily oral etoposide is as reasonable as any approach in the management of this disease in this patient population.

SPECIAL CONSIDERATIONS

A rising tumor marker (e.g., serum hCG or AFP) usually implies progressive cancer. However, marijuana, recent mononucleosis, or cross-reactivity with luteinizing hormone can cause double-digit hCG elevation. Benign liver disease can cause high AFP levels. A rising LDH should never be an indication for salvage chemotherapy. Also, a rising hCG or AFP in the absence of radiographic progression might indicate a sanctuary site relapse in the brain or a second primary in the contralateral testis. Patients with persistent elevated tumor markers after initial chemotherapy should not be considered for salvage chemotherapy unless there is a clear increase in hCG or AFP. This is especially true for patients with advanced disease presenting with serum hCG higher than 50,000 mIU/mL. Such patients will have a rapid descent in hCG after the first two courses and then have a plateau in further decline. It might take several months postchemotherapy to normalize an hCG in this patient population.

Radiographic progression with normal markers might indicate a growing teratoma rather than progressive germ cell cancer.

Late relapse (> 2 years postchemotherapy) occurs in 2% to 3% of patients. Disease in these patients is rarely curable with any form of salvage chemotherapy in the absence of surgery. Resection, if feasible, is the preferred option.

Progressive primary mediastinal nonseminomatous germ cell tumors are particularly difficult to cure with salvage therapy. Standard-dose salvage therapy will virtually always fail to produce a durable remission. Options are high-dose chemotherapy or surgical resection of a localized relapse.

CONCLUSION

Patients with relapsing disease after being managed with cisplatin combination chemotherapy are still curable, but it is very complicated. It is recommended that such patients be seen, or at least consulted, at tertiary centers with surgical and medical oncology expertise in germ cell tumors.

KEY POINTS

- Optimal strategy for management of relapse after initial cisplatin combination chemotherapy can be complicated.
- Occasionally localized relapsed disease can be cured with salvage surgery rather than salvage chemotherapy.
- Standard-dose cisplatin-combination salvage chemotherapy incorporates active drugs not previously utilized.
- Paclitaxel plus ifosfamide plus cisplatin or vinblastine plus ifosfamide plus cisplatin are examples of standard-dose salvage chemotherapy.
- High-dose chemotherapy with carboplatin plus etoposide with peripheral blood stem cell transplant has a high cure rate with acceptable toxicity.
References


