Long-term administration of single-agent carboplatin (AUC 4) for advanced testicular seminoma safely achieved complete response in an 80-year-old man with chronic heart failure: A case report

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Abstract

Carboplatin is often used instead of cisplatin as an alternative treatment for advanced testicular cancer. However, the safety, optimal dose, and optimal duration of this agent are unclear in patients with cardiac complications. We report the safety and effectiveness of long-term single-agent carboplatin for the treatment of testicular cancer in a patient with chronic heart failure (CHF). An 80-year-old man was referred to our institution for evaluation of painless swelling of the left scrotum. Computed tomography revealed lung metastases. Left radical inguinal orchiectomy was performed, and pathologic examination revealed a pure seminoma. Because he had CHF, there was high possibility of onset of acute heart failure secondary to fluid administration. Thus, single-agent carboplatin (AUC 4) was selected for therapy. A complete response was achieved after 8 of 13 cycles, and no serious adverse events occurred, including cardiac problems. Neither recurrence nor metastasis was detected during the 6-month follow-up. Low-dose, long-term carboplatin is likely effective for patients who are unfit for cisplatin administration because of comorbidities, especially CHF.

Introduction

Carboplatin is often used instead of cisplatin as an alternative key drug to treat advanced testicular cancer in patients unable to undergo cisplatin therapy due to comorbidities, including chronic heart failure (CHF).[1-5] Although single-agent carboplatin therapy is effective for advanced testicular cancer in some patients, the optimal dose and duration for the maximum therapeutic response with minimal adverse effects are very controversial.[6-8] Additionally, few reports have described the safety of carboplatin for patients with cardiac complications, especially CHF. We report the safety and effectiveness of long-term administration of single-agent carboplatin (AUC 4) for advanced testicular cancer in an 80-year-old man with CHF.

Case report

An 80-year-old man was admitted to hospital for replacement of the generator of his implanted pacemaker. Upon admission, he was referred to our institution for evaluation of painless swelling of the left scrotum. Chest radiography showed an approximate 3-cm mass lesion in the right lower lung (Fig. 1). Computed tomography (CT) of the lung, abdomen, and pelvis revealed a 7.0 × 10.0 × 11.5-cm left testicular tumour and multiple lung metastases (Fig. 2).

A left radical inguinal orchiectomy was performed, and pathologic examination revealed a pure seminoma. We noted the patient's serum markers, including his total human chorionic gonadotropin (total hCG), lactate dehydrogenase (LDH), and alpha-fetoprotein (AFP) (Table 1). The seminoma was stage IIIB and had a good prognosis according to the 2009 TNM classification for genitourinary tumours and the International Germ Cell Consensus Classification.[9] The estimated creatinine clearance showed renal insufficiency (49.7 mL/min). The patient had left ventricular dilatation, and his blood level of brain natriuretic peptide (BNP) was 456 pg/mL (normal level <18.4 pg/mL) secondary to a 10-year history of chronic, severe aortic regurgitation. Although he had no signs or symptoms of heart failure, such as dyspnea, angina, or fatigue, he was diagnosed with CHF based on the European Society of Cardiology Guidelines.[10]

Although cisplatin-based chemotherapy was an appropriate treatment with respect to his good performance status of 0 and stable clinical condition, there was a high possibility of acute heart failure secondary to the administration of a large amount of fluid.[11,12] Thus, single-agent carboplatin therapy (AUC 4) was selected after considering the balance between the therapeutic efficacy and potential for adverse effects. After 8 cycles of this therapy, the patient achieved a complete response. Thereafter, 5 additional cycles were performed as maintenance therapy (Fig. 3).

The maximum hematological toxicity that occurred was neutropenia grade 2 and thrombocytopenia grade 1, accord-

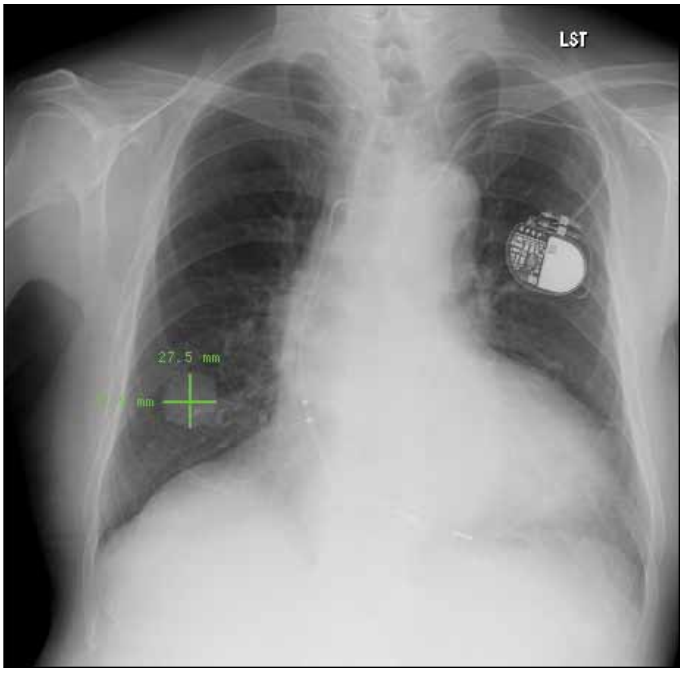

Fig. 1. Chest radiography showed an approximate 3-cm mass lesion in the right lower lung and left ventricular enlargement (cardiothoracic ratio, 69.1%).

ing to the Common Terminology Criteria for Adverse Events version 4.0. No signs of non-hematological toxicity were observed, such as nausea, diarrhea, neurotoxicity, or ototoxicity. Additionally, BNP level elevation, heart attack, and progression of renal dysfunction did not occur.

The patient was followed every 3 months by 2-^{18}Fluorodeoxy-D-glucose positron emission tomography (FDG-PET) in addition to examination of blood chemistry and tumour markers (total hCG, LDH, and AFP). Neither recurrence nor metastasis was detected during the 6-month follow-up.[13]

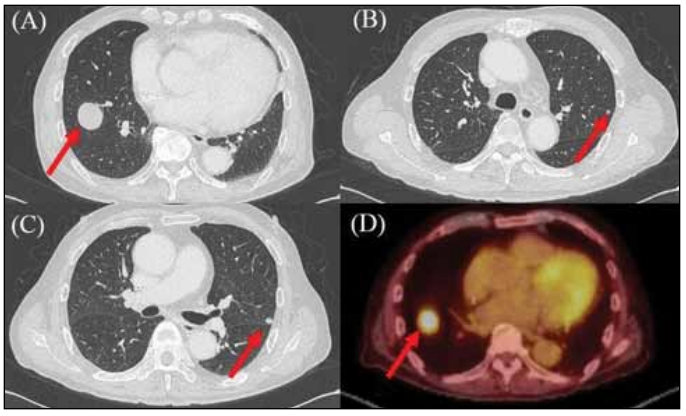

Fig. 2. Computed tomography of the lung before chemotherapy. A: Maximum dimensions of mass lesion in the right lower lung. B and C: Two metastases of the left lung. D: 2-^{18}Fluorodeoxy-D-glucose positron emission tomography (FDG-PET) of the lung corresponding to the maximum dimensions of the mass lesion in the right lower lung.

Table 1. Patient serum markers

Marker	Level	Normal level/range
Total hCG	6.0 mIU/mL	<5 mIU/mL
LDH	925 U/l	119–229 U/L
AFP	2.5 ng/mL	<6.2 ng/mL

Total hCG: Total human chorionic gonadotropin; LDH: lactate dehydrogenase; AFP: alpha-fetoprotein.

Discussion

This report illustrates 2 important clinical issues: carboplatin is safe for patients with asymptomatic CHF, and administration of single-agent carboplatin (AUC 4) for a long period of time is effective.

First, carboplatin is a safe agent for elderly patients with asymptomatic CHF. Because carboplatin does not require hydration during administration and produces fewer toxic adverse events than cisplatin, it is an optimal anticancer drug for patients who do not tolerate cisplatin.[1-5] Although carboplatin is considered safe and easy to use, it can induce cardiotoxicity via a mitochondrial-dependent apoptosis pathway, and a case of cardiac failure caused by carboplatin has been reported.[14,15] Thus, carboplatin should be carefully administered to patients with cardiac disease despite the fact that carboplatin-induced cardiac disease occurs at a low frequency. This is the first report to describe the administration of carboplatin every 4 weeks for 1 year to a patient with asymptomatic CHF without serious adverse events, including cardiac disease.

Second, long-term administration of single-agent carboplatin (AUC 4) is effective. Several reports have suggested the efficacy of single-agent carboplatin at doses of 5 to 12 AUC and treatment comprising 4 to 6 cycles. It is obvious that the likelihood of achieving complete response decreases

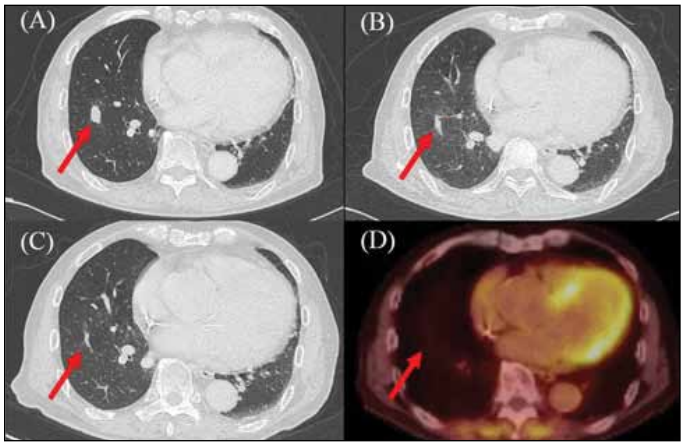

Fig. 3. Computed tomography of the lung after single-agent carboplatin chemotherapy showed a therapeutic effect as evidenced by the maximum dimensions of the lesion. A: After three cycles. B: After five cycles. C: After eight cycles. D: 2-^{18}Fluorodeoxy-D-glucose positron emission tomography (FDG-PET) of the lung 6 months after 13 cycles of chemotherapy.

as the stage of metastatic testicular cancer increases and that the risk of adverse events increases with the dose intensity. However, the relationship among the dose intensity, total number of cycles, and treatment outcome (including the rate of relapse) is very controversial.[4-8,16] Although there is no strict evidence for the efficacy of prolonged administration of carboplatin, including maintenance therapy, long-term carboplatin at 4 AUC may achieve therapeutic efficacy with minimal occurrence of serious adverse events.

Conclusion

Long-term therapy with single-agent carboplatin (4 AUC) is effective, has a low rate of adverse events, and is safe in patients with asymptomatic CHF. Although a low dose was very effective in the present case, it may not always be effective in other patients. Therefore, additional reports should be accumulated to determine which patients are the best candidates for low-dose single-agent carboplatin and what administration method is best to achieve a maximum therapeutic effect and minimal adverse events.

Competing interests: Authors declare no competing financial or personal interests.

This paper has been peer-reviewed.

References

1. Lichtman SM, Wildiers H, Launay-Vacher V, et al. International Society of Geriatric Oncology (SIOG) recommendations for the adjustment of dosing in elderly cancer patients with renal insufficiency. *Eur J Cancer* 2007;43:14-34. http://dx.doi.org/10.1016/j.ejca.2006.11.004
2. Horwich A, Dearnaley DP, Duchesne GM, et al. Simple nontoxic treatment of advanced metastatic seminoma with carboplatin. *J Clin Oncol* 1989;7:1150-6.
3. Sakaeda T, Kadoyama K, Okuno Y. Adverse event profiles of platinum agents: Data mining of the public version of the FDA adverse event reporting system, AERS, and reproducibility of clinical observations. *Int J Med Sci* 2011;8:487-91. http://dx.doi.org/10.7150/ijms.8.487
4. Wheater MJ, Manners J, Nolan L, et al. The clinical features and management of testicular germ cell tumours in patients aged 60 years and older. *BJU Int* 2011;108:1794-9. http://dx.doi.org/10.1111/j.1464-410X.2011.10252.x
5. Ismaili N, Naciri S, Afqir S, et al. A rare case of advanced testicular seminoma in a 78-year-old man managed successfully with carboplatin based chemotherapy: A case report. *Cases J* 2008;1:357. http://dx.doi.org/10.1186/1757-1626-1-357
6. Tookman L, Rashid S, Matakidou A, et al. Carboplatin AUC 10 for IGCCCG good prognosis metastatic seminoma. *Acta Oncol* 2013;52:987-93. http://dx.doi.org/10.3109/0284186X.2012.714078
7. Bokemeyer C, Kollmannsberger C, Stenning S, et al. Metastatic seminoma treated with either single agent carboplatin or cisplatin-based combination chemotherapy: A pooled analysis of two randomised trials. *Br J Cancer* 2004;91:683-7.
8. Gore M, Mainwaring P, A'Hern R, et al. Randomized trial of dose-intensity with single-agent carboplatin in patients with epithelial ovarian cancer. London Gynaecological Oncology Group. *J Clin Oncol* 1998;16:2426-34.
9. Albers P, Albrecht W, Algaba F, et al. EAU guidelines on testicular cancer: 2011 update. *Eur Urol* 2011;60:304-19. http://dx.doi.org/10.1016/j.eururo.2011.05.038
10. Dickstein K, Cohen-Solal A, Filippatos G, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur Heart J* 2009;19:2388-442.
11. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: Evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 2001;56:M146-56. http://dx.doi.org/10.1093/gerona/56.3.M146
12. Balducci L, Colloca G, Cesari M, et al. Assessment and treatment of elderly patients with cancer. *Surg Oncol* 2010;19:117-23. http://dx.doi.org/10.1016/j.suronc.2009.11.008
13. Bachner M, Loriot Y, Gross-Goupil M, et al. 2-(1)(8)fluoro-deoxy-D-glucose positron emission tomography (FDG-PET) for postchemotherapy seminoma residual lesions: A retrospective validation of the SEMPET trial. *Ann Oncol* 2012;23:59-64. http://dx.doi.org/10.1093/annonc/mdr052
14. Cheng CF, Juan SH, Chen JJ, et al. Pravastatin attenuates carboplatin-induced cardiotoxicity via inhibition of oxidative stress associated apoptosis. *Apoptosis* 2008;13:883-94. http://dx.doi.org/10.1007/s10495-008-0214-9
15. Sakai T, Yoshikawa K, Nosaka S, et al. A case report of cardiac failure caused by the new anti-neoplastic agent 'carboplatin' [in Japanese]. *Masui* 1993;42:756-60.
16. Krege S, Boergermann C, Baschek R, et al. Single agent carboplatin for CS IIA/B testicular seminoma. A phase II study of the German Testicular Cancer Study Group (GTCSG). *Ann Oncol* 2006;17:276-80. http://dx.doi.org/10.1093/annonc/mdj039

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