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LETTER TO THE EDITOR

Lenalidomide in patients with cisplatin-refractory and multiply relapsed germ cell tumors

Karin Oechsle · Carsten Bokemeyer · Friedemann Honecker

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Abstract
Objective Treatment options are still limited in patients with cisplatin-refractory and multiply relapsed germ cell tumors. We evaluated the efficacy and tolerability of lenalidomide within a compassionate use concept.
Patients and methods Four patients multiply relapsed after platin-based chemotherapies without any further standard treatment option received 25 mg lenalidomide orally on days 1–21 of a 28-day cycle.
Results All four patients were pretreated with a median number of seven lines of previous chemotherapy (range 4–8), all including platin-based high-dose chemotherapy. After 4 weeks of lenalidomide treatment all patients had progressive disease with increase in serum tumor markers and progression in computed tomography. Median survival time was 8 weeks (range 5–17). The toxicity profile was favorable. No severe toxicities related to lenalidomide occurred in these patients.
Conclusion Lenalidomide was well tolerated and showed efficacy in heavily pretreated patients with cisplatin-refractory and multiply relapsed germ cell tumors.

Keywords Germ cell tumor · Lenalidomide · Cisplatin refractory · Relapsed

K. Oechsle (✉) · C. Bokemeyer · F. Honecker
Departments of Oncology, Hematology, Bone Marrow Transplantation and Pneumology, University Medical Center Eppendorf, Martinistr. 52, 20246 Hamburg, Germany
e-mail: k.oechsle@uke.hamburg.de

Introduction

With cisplatin-based chemotherapy, approximately 70–80% of patients with metastatic germ cell tumors can be cured today (Einhorn 1999; Hartmann et al. 1999). Patients, who are refractory to or relapse after first-line chemotherapy may still achieve long-term survival due to salvage chemotherapy in 30–50%. However, prognosis remains to be extremely poor in patients that progress during or after salvage chemotherapy (Beyer et al. 1997). Several cytotoxic drugs were evaluated for palliative treatment in this situation, but until now the number of effective treatment options is limited. Only low-dose oral etoposide, gemcitabine, paclitaxel, and oxaliplatin demonstrated single-agent efficacy in these patients (Miller and Einhorn 1990; Bokemeyer et al. 1999; Einhorn et al. 1999; Bokemeyer et al. 1996; Kollmannsberger et al. 2002; Fizazi et al. 2004). Therefore, the investigation of further agents with potential efficacy is important to increase treatment options and to extend overall survival time. In a previous phase-II trial, thalidomide had shown some efficacy, including marker decline in 33% of 15 heavily pretreated patients with metastatic germ cell cancer (Rick et al. 2006).

Therefore, we evaluated the efficacy and tolerability of the thalidomide-analog, lenalidomide, 25 mg daily on days 1–21 of a 28-day cycle in patients with treatment-resistant metastatic germ cell tumors with no further established treatment option.

Patients and methods

Patients with histologically confirmed seminomatous or non-seminomatous germ cell tumors and with relapse after cisplatin-based chemotherapy including relapse after

salvage high-dose chemotherapy, or progression during palliative chemotherapy were included in this compassionate use program. Patients had to be refractory to or have relapsed after all existing standard treatment regimen, including gemcitabine, oxaliplatin and paclitaxel, and drugs evaluated within present clinical trials at that time. Patients with measurable tumor progression at least one site in X-ray, ultrasound, computed tomography, or magnetic resonance imaging or a documented increase in alpha-feto protein (AFP) or β-human chorionic gonadotropin (β-HCG) were included. In addition, pretreatment evaluation consisted of medical history, pre-existing toxicities, physical examination, laboratory including blood cell counts, liver function parameters, creatinine clearance, and electrolytes. All patients were informed about the experimental character of the compassionate use of the drug and had to give written informed consent.

Lenalidomide was administered at a dosage of 25 mg daily orally on days 1–21 of a 28-day cycle. This dosing schedule has been successfully established in patients with relapsed or refractory multiple myeloma or non-Hodgkin's lymphoma. Concomitant treatment other than chemotherapy, including palliative irradiation, was left to the decision of the treating physician. During lenalidomide application, blood cell counts, and electrolytes were controlled weekly. Before every new cycle, medical history including toxicity evaluation, physical examination, routine laboratory, serum tumor markers, and tumor staging had to be performed. Patients responding to lenalidomide were planned to be treated until tumor progression. Treatment should be immediately stopped in case of grade-IV hematologic or non-hematologic toxicities according to the common toxicity criteria (CTC). If grade II or III toxicities occurred, the study treatment should be interrupted until reconstitution to grade 0 or I was documented. In case of grade II-toxicities, dose reduction to 15 mg daily was recommended.

Results

Between 12/07 and 02/08, four patients with median age of 47 years (range 27–58) received palliative treatment with lenalidomide. All patients were refractory to or had relapsed after platinum-based chemotherapy, with a median number of seven previous lines of chemotherapy (range 4–8) of which a median of three lines (range 1–6) were cisplatin- or carboplatin based. All had undergone carboplatin-based salvage high-dose chemotherapy and, in addition, one had previously undergone primary cisplatin-based high-dose chemotherapy. Median time from primary diagnosis was 15 years (range 2–22). At the time of primary diagnosis, prognosis according to the International Germ Cell Cancer Collaborative Group (IGCCCG) was good or intermediate in two patients each. The primary tumor was located in the testis in three and in the retroperitoneum in one patient, and histology was non-seminoma in three and pure seminoma in one patient. At the time, lenalidomide treatment was started, all patients presented with multiple metastases, most frequently located in the lungs (4 patients), retroperitoneal lymph nodes (3 patients), and the liver, distant lymph nodes or in the brain (1 patient each). An elevated AFP was seen in two patients (18,944, 4,253 kU/l), and LDH (median 996 U/l) and β-HCG (median 643 U/l) were elevated in all patients.

All patients received 25 mg lenalidomide daily for 21 days. One patient underwent concomitant palliative irradiation of his cerebral metastases. At the first revaluation after 4 weeks, progressive disease with increase in serum tumor markers and progression in computed tomography was observed in all patients and treatment was stopped. The median survival time from the start of treatment with lenalidomide was 8 weeks (range 5–17 weeks). Afterwards, one patient underwent two further lines of palliative chemotherapy without any response. The toxicity profile of lenalidomide was favorable. All cycles could be applied without any dose modifications. No severe toxicities related to lenalidomide occurred in these patients.

Discussion

Not withstanding the high-cure rate in patients with metastatic germ cell tumors due to platin-based combination chemotherapy in general, long-term survival rates in patients progressing during or after standard or high-dose salvage chemotherapy is <5% (Einhorn 1999). Therefore, the evaluation of new cytotoxic agents with potential efficacy is indicated to explore additional treatment options. As thalidomide had shown some activity with serological partial remission in 33% of the patients in a previous phase-II trial including a similar group of 15 patients, lenalidomide seemed a reasonable choice as an investigational substance (Rick et al. 2006). In the present evaluation, only patients with unfavorable prognostic characteristics and extensive previous therapy, including treatment with newer agents with proven activity, such as paclitaxel, oxaliplatin, and gemcitabine, have been included. Overall, the toxicity profile of lenalidomide was favorable in these heavily pretreated patients without any toxicities grade II/III/IV according to CTC possibly related to lenalidomide. However, lenalidomide as a single agent did not show any anti-tumor activity in these four cases of patients with refractory germ cell tumors, as all patients showed tumor progression during the first cycle of treatment. It has to be considered that the mechanism of action,

mainly anti-angiogenesis, immunomodulation, and modification of the tumor environment, may not be sufficient for activity as a single agent in patients with refractory solid tumors. Combinations with cytotoxic agents may be an alternative approach that might be synergistic in solid tumors and remains to be evaluated.

Even though the number of patients treated was small, lenalidomide does not seem to have major activity in a small number of patients with refractory or relapsed germ cell tumors and further evaluation of the substance as a single agent in this situation does not seem to be warranted.

Conflict of interest statement None.

References

Beyer J, Kingreen D, Krause M et al (1997) Long-term survival of patients with recurrent or refractory germ cell tumors after high dose chemotherapy. Cancer 79:161–168. doi:10.1002/(SICI)1097-0142(19970101)79:1<161:AID-CNCR23>3.0.CO;2-1

Bokemeyer C, Beyer J, Metzner B et al (1996) Phase II study of paclitaxel in patients with relapsed or cisplatin-refractory testicular cancer. Ann Oncol 7:31–34

Bokemeyer C, Gerl A, Schoffski P et al (1999) Gemcitabine in patients with relapsed or cisplatin-refractory testicular cancer. J Clin Oncol 17:512–516

Einhorn LH (1999) Treatment of testicular cancer: a new and improved model. J Clin Oncol 8:1777–1781

Einhorn LH, Stender MJ, Williams SD (1999) Phase II trial of gemcitabine in refractory germ cell tumors. J Clin Oncol 17:509–511

Fizazi K, Culine S, Chen I (2004) Oxaliplatin in non-seminomatous germ-cell tumors. Ann Oncol 15:1295. doi:10.1093/annonc/mdh307

Hartmann JT, Kanz L, Bokemeyer C (1999) Diagnosis and treatment of patients with testicular germ cell cancer. Drugs 58:257–281. doi:10.2165/00003495-199958020-00004

Kollmannsberger C, Rick O, Derigs H-G et al (2002) Activity of oxaliplatin in patients with relapsed or cisplatin-refractory germ cell cancer: a study of the German Testicular Cancer Study Group. J Clin Oncol 20:2031–2037. doi:10.1200/JCO.2002.08.050

Miller JC, Einhorn LR (1990) Phase II study of daily oral etoposide in refractory germ cell tumors. Semin Oncol 17:36–39

Rick O, Braun T, Siegert W, Beyer J (2006) Activity of thalidomide in patients with platinum-refractory germ-cell tumors. Eur J Cancer 42:1775–1779. doi:10.1016/j.ejca.2006.03.013