Preliminary Results of the GPO-Trial for Treatment of Non-Testicular Germ-Cell Tumors in Children and Adolescents

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Key Words

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Summary

Germ cell tumors account for a 3% mortality rate of childhood malignancies. The combined chemotherapy, vinblastine, bleomycin and cis-platinum, is probably associated with more toxicity and treatment-induced mortality in children. Based on pharmacokinetic findings concerning the renal elimination of bleomycin and the well known cis-platinum nephrotoxicity, these two drugs were given sequentially. In addition, the cumulative dose of bleomycin was limited to 180 mg/m². 61 patients entered the trial whereby 42 of these are evaluable. The chemotherapeutic regimen was well tolerated and was completed in 19 patients without treatment induced mortality and without evidence of pulmonary fibrosis. The treatment regimen seems to be successful despite the relatively low cumulative doses of vinblastine and bleomycin, as only 4 of 19 patients relapsed after a median observation period of 12 months.

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Schlüsselwörter

Ovarialtumoren
Keimzelltumoren
Bleomycin bei Kindern
Teratome

Zusammenfassung

Bösartige Keimzelltumoren machen 3% der Sterberate durch bösartige Tumoren im Kindesalter aus. Die bei Erwachsenen sehr erfolgreiche Chemotherapie aus Vinblastin, Bleomycin und Cis-Platinum ist wahrscheinlich bei Kindern mit einer erhöhten Nebenwirkungsrate und tödlichen Komplikationen behaftet. Aufgrund pharmakokinetischer Untersuchungen zur renalen Ausscheidung von Bleomycin und der bekannten Nephrotoxizität von Cis-Platinum werden in dem Therapieprotokoll diese Medikamente nur in Sequenz verabreicht. Zusätzlich wird die kumulative Bleomycindosis auf 180 mg/qm beschränkt. Von 61 gemeldeten Patienten erfüllten 42 die Bedingungen des Protokolls. Die Chemotherapie konnte bisher bei 19 Patienten beendet werden und wurde ohne therapiebedingte Mortalität und ohne Hinweise für eine Lungenfibrose toleriert. Das Behandlungskonzept erscheint trotz der geringen kumulativen Bleomycindosis

wirksam, da bisher nur 4 von 19 Patienten nach einer mittleren Beobachtungsdauer von 12 Monaten ein Rezidiv erlitten.

Germ cell tumors account for about 3 % of the mortality from childhood malignancies [14]. Fully malignant germ cell tumors with the exception of immature teratomas and seminomas/dysgerminomas have been associated with a poor outcome of less than 10% cure rate despite radical surgery, radiation and chemotherapy with vincristine (VCR), actinomycin D (AMD), and cyclophosphamide (CYC) [9,10,13]. The combination of vinblastine (VBL), bleomycin (BLEO) and cis-platinum (DDP) has improved the prognosis for testicular tumors in adults and also in children [2, 8, 11]. There is evidence, however, that this chemotherapeutic regimen is associated with more toxicity and even treatment induced mortality in children [2, 3, 5, 12] as compared to the fairly satisfactory tolerance in adults. According to some reports approximately half of the children so treated developed pulmonary fibrosis with lethal outcome [2, 5] so that it was concluded that further use of bleomycin in children is to be abolished [2] , or at least the combination of cis-platinum and bleomycin is to be avoided [1].

Treatment Strategy of the GPO-Trial

Based on pharmacokinetic findings concerning the renal elimination of bleomycin [6] and the well known cis-platinum

nephrotoxicity, cis-platinum is administered not in combination with bleomycin but sequentially on days 4 to 8 after the initial administration of bleomycin on days 1 to 3. In addition the cumulative dose of bleomycin is limited to 180 mg/m². Since the prognosis of germ cell tumors with extratesticular primary site is poor [4, 7], the treatment strategy is stratified according to site, stage, and histology:

All patients with fully malignant nonseminomatous germ cell tumors receive 4 courses of VBL (3 mg/m², days 1 and 2), BLEO (15 mg/m² as 24 h continuous infusion, days 1-3), and DDP (20 mg/m², days 4-8); following 4 courses of chemotherapy a second look laparotomy is performed to remove residual tumor.

Fully malignant nonseminomatous germ cell tumors of the ovaries, Figo stage II-IV and all tumors with primary extragonadal site are, following second look surgery, continued on chemotherapy and receive 4 courses of VP 16 (100 mg/m², days 1-3), ifosfamide (1500 mg/m² with mesna uroprotection, days 1-5), and DDP (20 mg/m², days 1-5).

(3) Extragonadal seminomas and dysgerminomas of the ovaries, stage II-IV, are to receive 4 courses of VBL, BLEO and DDP, radiation is only applied in patients with incomplete remission under chemotherapy or recurrent disease.

(4) More differentiated teratomas of the immature subtype (grades 2 and 3) are treated with combination of VBL

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(3 mg/m², days 1 and 2), AMD (0.5 mg/m², days 1-3) and CYC (800 mg/m², day 3).

(5) Differentiated teratomas (grades 0 and 1) and dysgerminomas, Figo stage I, are carefully followed at short intervals after surgery and do not receive further chemotherapy unless there is recurrent disease.

The trial was opened January 1, 1983, and by September 1,

1984, 61 patients were entered; 42 of these patients (12 male, 30 female) were considered protocol patients according to the criteria of the trial.

Sacroccygeal Teratomas

7 out of 19 children (age 0-10 years) had a fully malignant tumor at the time of diagnosis. 2 additional patients with a differentiated teratoma at the time of initial diagnosis developed a local recurrence as yolk sac tumor. In both of these patients the coccygeal bone had not been resected during the primary surgery. In 9 patients who received chemotherapy there have been to date 3 relapses, 6, 10, and 16 months following initiation of treatment. The median period of observation in this group was 10 months.

Ovarian Tumors

18 patients presented with ovarian tumors. According to histological evaluation 5 were classified as yolk sac tumors, 3 as dysgerminomas, and 10 as differentiated teratomas. Only 1 of 8 patients who had received chemotherapy developed recurrent disease at 11 months. The median period of observation in this group was 12 months.

Other Sites

5 patients presented with germ cell tumors in other primary sites: neck (1 patient), mediastinum (1 patient), stomach (1 patient), pelvis (2 patients). 2 of these children received chemotherapy for the histologic category of a yolk sac tumor and are both in complete remission 6 and 12 months following diagnosis and initiation of treatment.

Toxicity

The chemotherapy regimen is associated with the known side effects of chemotherapeutic agents; however, there has been no evidence of pulmonary fibrosis and no treatment-induced mortality among 19 patients who have completed chemotherapy at present.

Conclusion

The chemotherapeutic regimen in the GPO germ cell tumor trial is well tolerated and has been completed in 19 patients without treatment-induced mortality and without evidence of pulmonary fibrosis. The treatment regimen seems to be successful despite the relatively low cumulative doses of VBL and BLEO, as unresectable tumor masses have responded with complete long lasting remission.

The strategy of second look surgery following 4 courses of chemotherapy has to be considered as an important part of the treatment since vital tumor has been detected in some surgical specimens despite clinical remission.

Since 2 children developed a local recurrence arising from the coccygeal bone following surgery of a mature teratoma the en bloc resection of differentiated teratomas along with the resection of the coccygeal bone appears to be essential. Especially the very unfavorable prognosis of sacroccygeal yolk sac tumors has considerably been improved with pro-tochemotherapy followed by tumor resection and adjuvant chemotherapy.

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