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High-dose chemotherapy with autologous hemopoietic stem cell transplantation in children with retinoblastoma. Literature review and case series

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Summary

Retinoblastoma (RB) is the most common malignant eye tumor in children accounting for 10-15% of all cancer cases in infants. In spite of generally good standard treatment results there is still a subgroup of high-risk patients with by unfavorable prognosis, which warrants the search for additional treatment strategies. These children may benefit from treatment intensification in form of high-dose consolidation with subsequent autologous hemopoietic stem cell therapy (auto-HSCT). We here describe a case series illustrating N. N. Blokhin Cancer Center experience in this area.

Materials and methods

In 2021 a total of 3 children with high-risk RB were treated in N. N. Blokhin Cancer Center receiving high-dose regimen consisting of carboplatin (total dose of 1250 mg/m^2), etoposide (1750 mg/m^2), and cyclophosphamide (6000 mg/m^2) with subsequent auto-HSCT.

Results

All 3 patients engrafted in day +11, +14, and +17 after auto-HSCT. The early post-transplant period was complicated by oral mucositis, neutropenic enterocolitis, and febrile neutropenia. One patient had a single episode of seizures due to hyponatremia. With a median follow-up of 6 (4-10) months two patients are alive and disease-free, one died due to disease progression.

Conclusions

The high-dose consolidation with subsequent auto-HSCT is a fea-sible option for high-risk RB patients. It is characterized by acceptable toxicity and is a potentially effective for disease control. In order to further evaluate the long-term results, there is a need for a larger prospective patient cohort. The multicenter study design may be beneficial in these settings.

Keywords

Autologous hematopoietic stem cell transplantation, retinoblastoma, children, high-dose chemotherapy.

Introduction

General issues

Retinoblastoma (RB) is the most common pediatric eye cancer developing from immature cells of the retina [1-3]. In infants it is most commonly associated with biallelic mutation of RB1 gene [4]. In these cases the tumor may involve one, as well as both, eyes and also may produce synchronous or metachronous ectopic lesions in the pineal gland (pineoblastoma). Based on extent of involvement these forms are classified as uni- bi- and trilateral [5]. The RB incidence is 1 in 15000-18000 newborn and about 5000 new cases are registered each year [6].

Most treatment programs in patients with RB combine different treatment modalities, which are chosen based in risk group and extent of tumor involvement [7, 8]. In high-risk patients the tumor spreads beyond the eye often developing ectopic metastatic lesions, which may become lethal if no systemic method is applied in addition to local control measures [9]. During the last few decades a number of methods were used to control the disease including systemic polychemotherapy (CT), external beam radiation therapy (EBRT) and other local treatment methods. However, these standard measures may still be ineffective in some cases, so we are ever in need of new global strategies aimed at survival improvement in high-risk RB.

High-dose chemotherapy with autologous hemopoietic stem cell transplantation in patients with RB

In developed countries most children with RB are referred to pediatric oncologist in early stages. Most advanced cases with extraocular and metastatic RB are therefore treated in developing countries. Most deaths in RB patients are due to metastatic disease, pineoblastoma development or secondary cancers, which are most often seen in patients with hereditary forms of disease. The treatment schedule is always personalized in accordance to individual tumor characteristics. Up to this moment the main therapeutic modalities are systemic polychemotherapy (PCT) and local one, which may be delivered as inraarterial chemotherapy (IAC) or intravitreal one (IVitC). There are also additional local control methods such as transpupillary thermotherapy (TTT), cryotherapy, and brachytherapy or enucleation, which may be performed in cases with optical nerve or choroidal invasion [10, 11].

Each of these methods has certain disadvantages and unwanted sequelae. Most clinics limit the use of external beam radiation therapy (EBRT) due to the risk of secondary cancers, facial bones growth disturbance and subsequent deformations. Enucleation is a radical surgical technique based on entire eye removal [12]. While chemoreduction (tumor shrinking in response to systemic chemotherapy) and local control measures are effective in patients with intraocular RB and have fewer adverse effects, they are less effective in patients high-risk disease characterized by initial extraocualr disease, tumor relapse involving extra- or intraocular structures (includ-ing distant metastases), tumor invasion of the optic nerve resection line, trilateral RB. As a result, high-risk patients may need more aggressive treatment modalities [10-13]. Therefore, there is still an ongoing search for more effective strategies able to improve long-term survival and quality of life in this cohort.

RB is a highly chemosensitive tumor with exponential log kill curve in tumor cell cultures, so dose-intensive consolidation regimens are expected to increase the overall treatment effectiveness. High-dose chemotherapy (HDCT) is being considered a viable option [14-17]. However, this method is associated with some drawbacks due to its toxic effects, primarily profound myelosuppression, which may lead to serious or even fatal complications if no attempts for bone marrow reconstitution *via* cryopreserved autologous hemopoietic stem cells (bone marrow or peripheral blood precursors) reinfusion are taken. Autologous hemopoietic stem cells transplantation (auto-HSCT) is the most effective measure to limit secondary myelotoxicity and allows using much higher peak doses of cytostatics potentially increasing RB treatment effectiveness [16].

A number of researchers have demonstrated different high-dose regimens effectiveness in auto-HSCT settings. These regimens are used as consolidation in patients with high-risk pediatric solid tumors as part of a multidisciplinary approach incorporating also surgical treatment and standard dose chemotherapy [12], in some cases they may also help to avoid bilateral enucleation preserving the vision in RB patients.

There is currently no consensus on optimal treatment regimen in late stage RB, although most experts agree on the use of several drugs in combination. These drugs, which may be potentially effective in RB patients, include platinum agents (carboplatin and cisplatin), etoposide, vincristine, cyclophosphamide and anthracyclines [18, 19]. Vincristine, etoposide and carboplatin are characterized by better eye penetration and are therefore most often used in conditioning regimens prior to auto-HSCT.

World experience with auto-HSCT in the RB patients

The HDCT with auto-HSCT is now being used in patients with high-risk RB for more than 20 years. The first patient cohort was described in 1997 by French researchers from Institut Curie (Paris). The HDCT was performed as consolidation for high-risk patients (initially extraocular disease, relapse or tumor invasion of optical nerve resection line). A total of 25 patents received a regimen consisting of carboplatin (250 mg/m^2/day from day 1 day 5 in 6 initially high-risk patients after enucleation and standard-dose CT and 250 mg/m^2/day in 19 patients with chemosensitive relapse), etoposide (350 mg/m^2/day from day 1 to day 5), and cyclophosphamide (1.6 g/m^2/day from day 2 to day 5) with subsequent autologous stem cells reinfusion. The 3-year disease-free survival was 67.1%. In 7 of 19 patients with relapse it developed in central nervous system. All patients with CNS relapse except one died of disease progression. The main toxic complications were hematological toxicity and gastrointestinal mucositis (oral mucositis, enterocolitis). Also, 2 of 13 patients developed grade III-IV ototoxicity. In one case a grade I acute re-versible cardiotoxicity was

registered. Therefore, while high-dose regimen consisting of carboplatin, etoposide and cyclophosphamide seemed a feasible strategy in high-risk RB patients, especially those with bones and bone marrow involvement, it did not improve the results in cases with CNS involvement [20].

In 2003, a group of German researchers published their data on auto-HSCT outcome in 5 RB patients, 4 of them with bone marrow metastases and one with extraorbital involvement. All patients have achieved response after previous enucleation and standard-dose chemotherapy, a child with extraorbital tumor also received EBRT. In 4 cases the conditioning regimen consisted of thiotepa (900 mg/m^2), etoposide (40 mg/kg), and carboplatin (1.5 g/m^2), and in 1 case it included carmustine (300 mg/m^2), cyclophosphamide (6.8 g/m^2), and etoposide (1.6 g/m^2). A rapid hemopoiesis reconstitution was observed in all 5 cases. Main toxic complications were mucositis and cytopenia with consequent infections. None of the patients died due to regimen toxicity or experienced any long-term sequelae. A patient with initial extrorbital disease developed a relapse with meningheal involvement 10 months after auto-HSCT, but was salvaged by surgery and standard-dose chemotherapy and remained in remission after 105 months follow-up. Four other patients were still in remission 107, 57, 9, and 8 months after auto-HSCT. The conditioning regimen with thiotepa, etoposide and carboplatin may be a good option for children with extrabulbar or disseminated chemosensitive RB [21].

In 2021, a group of authors from the Faculty of Medicine, University of Indonesia published a review on available data in auto-HSCT for high-risk RB patients [22]. A total of 35 publications describing 160 patients were included. After auto-HSCT 108 of 160 (67.5%) patients are alive and disease free at the last follow-up. The secondary cancer developed in 16 of 160 (10%) patients, which is a comparably low rate. The most common side effects were hematological and gastrointestinal toxicity. As a whole, 41 of 160 (25.6%) died with signs of active disease due to primary CNS involvement (in 25 of 41; 60.9%), disease relapse (12 of 41; 29.3%), or secondary cancer (3 of 41; 7.3%). Only in 1 of 41 (2.4%) cases there was evident metastatic involvement outside CNS. Only 11 of 160 (6.7%) were alive, but not disease-free, at the last fol-low-up. According to this review, the use of HDCT with subsequent auto-HSCT is effective in patients with disseminated RB as 108 of 160 (67.5%) of auto-HSCT recipients stayed alive and disease-free. It corresponds to the data published in previous review by *Jaradat I. et al.* (2012) [23].

Russian experience with auto-HSCT in children with retinoblastoma

There are several large Russian centers treating most children with RB, i.e., the Helmholtz National Medical Ophthalmology Research Center, S.N. Fedorov National Medical Research Center for Eye Microsurgery, and Research Institute of Pediatric Oncology and Hematology at the N.N. Blokhin National Medical Research Center of Oncology. However, only the latter institution performed HDCT with auto-HSCT in these patients.

There is a description of earlier (2001-2008) experience of auto-HSCT performed in a cohort of 15 RB patients in the Institute of Pediatric Oncology and Hematology at the N.N. Blokhin National Medical Research Center of Oncology. The treatment program included IVitC, EBRT, and high-dose consolidation with busulfan and melphalan followed by auto-HSCT. During the follow-up 1 of 15 patients died of sepsis and 7 of disease progression with CNS involvement. Seven patients are currently alive (5 children with stage II, one with stage IIIa, one with stage IIIb). The new strategy allowed to double the disease- and event-free survival rate of RB patients. The overall survival in high-risk group (optical nerve resection line invasion, extrascleral spread of the tumor) reached 71.4%. The researchers concluded that HDCT with auto-HSCT is an effective method in patients with stage II and III, although more effective options are still warranted for children with disseminated RB [24].

Clinical cases

We present a series of 3 clinical cases of children (aged 3-6 years) with high-risk RB receiving HDCT with auto-HSCT treated at the Pediatric Hematology and Oncology Department (BMT unit) at N.N. Blokhin National Medical Research Center of Oncology (February to October 2021). All the patients achieved remission prior to HSCT after surgery and standard-dose systemic polychemotherapy. The patients' characteristics are listed in Table 1. Patient 1 had initially demonstrated extraocular tumor growth by the optical nerve, there were also tumor cells in resected margin; patient 2 had initially disseminated disease with cervical lymph nodes involvement, and patient 3 had bilateral disease with extrabulbar and intracranial penetration of the right eye tumor *via* optical nerve with involvement of ipsilateral chiasma and optical tract.

Table 1. Initial characteristics of our retinoblastoma patients and autologous HSCT details

Patient	Sex	Age, years	Conditioning regimen	Number of CD34+ cells infused (×10^6/kg of body weight)
1	Male	6	Carboplatin 1250 mg/m^2, Etoposide 1750 mg/m^2, Cyclophosphamide 6000 mg/m^2	4.93
2	Male	3	Carboplatin 1250 mg/m^2, Etoposide 1750 mg/m^2, Cyclophosphamide 6000 mg/m^2	2.4
3	Male	3	Carboplatin 1250 mg/m^2, Etoposide 1750 mg/m^2, Cyclophosphamide 6000 mg/m^2	1.2

In order to successfully collect autologous peripheral stem cells according to local standards, all the patients received granulocyte colony-stimulating factor (G-CSF). Stem cell mobilization started 14 days prior to the next chemotherapy course upon recovery of the blood counts. G-CSF was injected subcutaneously for 4-7 days at 5-10 mcg/kg/day, the last dose applied 2-4 hours prior to apheresis procedure. The median yield of CD34+ cells was 2×10^6 /kg body mass.

Patient 1 is a six-year-old child with left-sided retinoblastoma. In October 2020, eye enucleation was performed, followed by microsurgical removal of the left optical nerve by orbitozygomatic approach (pathological study showed tumor cells at the resection line of optical nerve, thus corresponding to high-risk case), with 6 subsequent chemotherapy courses. No staging was performed at the clinic, where the patient was initially treated.

Patient 2, three-year-old, was diagnosed with left-sided retinoblastoma TxNxMx. In October 2020, left eye enucleation was performed. Subsequent staging showed disease progression with metastatic involvement of cervical lymph nodes. Therefore, 4 chemotherapy courses according to NB 2004 protocol and 2 CVC courses were performed. The patient was re-staged as TxN1.

Patient 3, three-year-old, manifested with bilateral RB: OD – group E, stage T4N0M1; OS – Group B, stage T1N0M1. He received a complex treatment program consisting of 5 systemic chemotherapy courses and 5 courses of intrathecal chemotherapy (methotrexate + prednisolone/thiotepa), surgical treatment (right-sided bone plastic pterional craniotomy with prechiasmal optical nerve resection and eye enucleation) performed in December 2020.

Pre-transplant consolidation regimen consisted of carboplatin 1250 mg/m^2, etoposide 1750 mg/m^2, and cyclophosphamide 6000 mg/m^2. Patients 1 and 2 have tolerated the high-dose regimen well. In patient 3, some complications were registered, i.e., anorexia, nausea, vomiting, and an episode of seizures in presence of arterial hypertension and hyponatremia, the most likely causes of this neurological disorder. The seizures were canceled by anticonvulsants, antihypertensive therapy and infusion of electrolytes. No signs of hemorrhage or ischemia were seen on the brain CT scan.

The HSCT procedure was well tolerated in all cases. During early post-transplant period, all patients received standard supportive therapy (decontamination, prophylaxis of herpesvirus infection, pneumocistic and fungal infections). The leukocyte engraftment was registered on day 11, 14, and 17; in all the cases, G-CSF was injected subcutaneously (5 μg/kg/day). All the patients became transfusion-independent since 14 days post-transplant. There were complaints for nausea and vomiting over the early post-transplant period. In all the cases, distinct infectious and toxic complications were developed, i.e., grade 1-3 oral mucositis, grade 2 neutropenic enterocol-itis, and febrile neutropenias. Central line-associated bloodstream infection (CLABSI) was registered in one case. All these complications were controlled by standard therapies. All the patients were subsequently discharged in good clinical condition. The median follow-up is currently 6 (4-10) months. The clinical outcomes of the transplants are shown in Table 2.

Discussion

High-dose consolidation chemotherapy was performed in 3 children with high-risk RB admitted to N.N. Blokhin National Medical Research Center of Oncology. All the patients have well tolerated the treatment. The blood counts recovered relatively early. All complications were successfully treated with standard antibacterial therapy within 14 days post-transplant. Then the patients were discharged from the BMT unit to the Somatic Department for further follow-up. The third patient developed a progressive CNS disease 6 months after auto-HSCT and subse-quently died. Patients 1 and 2 have currently no signs of disease progression at the median fol-low-up of 6 (4-10) months.

Since the dose-intensive therapy is recommended in disseminated RB [9], we used a conditioning regimen including carboplatin, etoposide and cyclophosphamide. This schedule has already been successfully used in international cohorts and proved to be effective in cases of disseminated disease [14, 16-19]. The patients included in our series have also well tolerated the high-dose regimen which corresponds to the published data [20, 23, 26] and may confirm safety of HDCT procedure, even in heavily pretreated children with lower performance score.

Table 2. Results of autologous HSCT in the patients included in the study

Patients	WBC reconstitution, day after auto-HSCT	Plt reconstitution, day after auto-HSCT	Complications of conditioning regimen	Complications in early post-transplant period					Outcome
				Febrile neutropenia	Oral mucositis	Neutropenic enterocolitis	CLABSI	Malnutrition state	
1	+11	+16	none	7 days	St.1	none	+	+	Alive, in remission
2	+17	+19	none	8 days	St.2	St.2	none	+	Alive, in remission
3	+14	+17	Episode of seizures	2 days	St.3	St.2	none	+	Died of disease progression

Unfortunately, there is lack of effective and curative treatment methods for the patients with CNS involvement despite multiple options used by different centers, with HDCST with auto-HSCT included [9, 20]. We must search for new approaches, or modify the existing methods in order to improve our results in high-risk RB. Our experience shows that concentration of several RB patients with high-risk disease at a single center provides the necessary experience allowing most effective treatment [12, 20-23, 25].

During the last decade, some major shifts occur in the complex treatment of children with RB. Auto-HSCT became an integral part of the overall treatment strategy. Our case series demonstrate acceptable toxicity of this treatment mode, with side effects observed, mostly, in the form of gastrointestinal toxicity. No transplant-related mortality was registered. Therefore, this approach may be considered relatively safe. We should, however, keep in mind that clinical re-sults in patients with CNS metastases are still unsatisfactory. Hence, we should perform more strict selection of the candidates for auto-HSCT. Of course, in order to obtain more reliable results, much larger groups should be studied, which is more likely in context of multicenter studies coordinated on national level.

Conclusion

Auto-HSCT may be considered a feasible, effective and well-tolerated consolidation option for patients with high-risk RB. A larger cohort study with longer follow-up is required to accurately evaluate its effectiveness. This may be achieved in multicenter cooperation.

Conflicts of interest

None reported.

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Высокодозная химиотерапия с аутологичной трансплантацией гемопоэтических стволовых клеток при ретинобластоме у детей. Обзор литературы и демонстрация клинических случаев

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Резюме

Ретинобластома (РБ) – самое частое злокачественное новообразование (ЗНО) органа зрения у детей, составляет 10-15% от всех ЗНО детей первого года жизни. Несмотря на наличие стандартных подходов к лечению детей с РБ, в ряде случаев стандартные методы могут оказаться неэффективными, что требует поиска новых стратегий для улучшения выживаемости у детей группы высокого риска. В качестве интенсификации может использоваться высокодозная химиотерапия с последующей аутологичной трансплантацией гемопоэтических стволовых клеток (ауто-ТГСК). Цель нашей работы – демонстрация опыта НМИЦ онкологии им. Н. Н. Блохина на примере случаев ауто-ТГСК у пациентов с РБ.

Материалы и методы

В 2021 г. в НИИ детской онкологии и гематологии НМИЦ онкологии им. Н. Н. Блохина 3 пациента с РБ высокой группы риска получили в режиме кондиционирования: Карбоплатин 1250 мг/кв.м., Этопозид 1750 мг/кв.м., Циклофосфамид 6 гр/кв.м. с последующей ауто-ТГСК.

Результаты

Восстановление гемопоэза произошло на 11, 14 и 17 сутки после ауто-ТГСК. Осложнения раннего посттрансплантационного периода: орофарингеальный мукозит, нейтропенический энтероколит, фебрильная нейтропения. В периоде кондиционирования у одного пациента зафискирован эпизод тонико-клонических судорог на фоне гипонатриемии, эпизод купирован, более не повторялся. У одного пациента констатирована прогрессия заболевания, что привело к летальному исходу. Два пациента – без признаков рецидива. Медиана наблюдения 6 (4-10) месяцев.

Выводы

Ауто-ТГСК для пациентов с РБ группы высокого риска может рассматриваться как консолидация, в виду хорошей переносимости и эффективности. Требуется включение в исследование большего числа пациентов, длительное наблюдение, а также обмен опытом между трансплантационными центрами.

Ключевые слова

Аутологичная трансплантация гемопоэтических стволовых клеток, ретинобластома, дети, высокодозная химиотерапия.