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CONSENSUS ON INDICATIONS FOR HEMATOPOIETIC STEM CELL TRANSPLANTATION IN PEDIATRICS. UPDATE 2020: CENTRAL NERVOUS SYSTEM TUMORS AND RETINOBLASTOMA

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SUMMARY

The indications for hematopoietic stem cell transplantation in solid tumors in children do not change a lot since our first Brazilian consensus publication in 2009. In this article, we are going to review indications to hematopoietic stem cell transplantation in solid tumors.

For the consensus, a review was made using the most relevant articles, and a series of meetings was done to discuss the recommendations.

In some indications, autologous transplantation is no longer used as a treatment option, however we chose to review these diseases and keep them as a non-recommendation.

In this article we are going to review CNS tumors and retinoblastoma

Keywords: Central nervous system; Medulloblastoma, Retinoblastoma; Stem Cell Transplantation

METHODS

The literature review for the elaboration of this consensus was based on indexed articles, preferably published in the last ten years, including what was published in the annals of national and international congresses. However, considering that many diseases have few new publications, some diseases have older articles.

Personal experience of the service or of the country,

even if not published, can be used to justify indications for transplantation, if the data are properly presented.

RECOMMENDATIONS

All recommendations are summarized in table one, and more details about each indication is in the following text

TUMORS OF THE CENTRAL NERVOUS SYSTEM

Considering a significant proportion of embryonal tumors affecting young children, the High dose Chemotherapy are large explored in the literature in an attempt to avoid neurocognitive and endocrinological sequelae radiation induced.

Autologous transplantation was the most studied. Most conditioning schemes use Thiotepa (Triethylenethiophosphoramide)⁽¹⁾.

Medulloblastoma, in infants and children under four years are the most studied. Particularly tumors that present unfavorable histology and molecular changes may benefit from this approach.⁽¹⁻³⁾

Patients with late recurrence, can also benefit from autologous transplantation, although not indicated in chemoresistant or bulky disease.^(4,5)

The therapeutic option is Tandem (autologous stem cell transplant) transplantation: 2-3 courses, with Thiotepa being well tolerated (6) in combination or not with Carboplatin or single transplant with sequential use of Thiotepa, carboplatin and Etoposid. A retrospective analysis of recurrent primitive chemosensitive neuroectodermal tumors (PNET) also showed good cure rates in patients undergoing sequential Thiotepa courses⁽⁷⁾.

Other tumors such as atypical rhabdoid teratoid, an embryonic tumor, can sometimes become difficult to classify and are commonly confused with medulloblastoma or a primitive neuroectodermal tumor. Standard treatment involves surgical resection followed by radiotherapy and systemic chemotherapy, but in children under 4 years old - most patients when considering a tumor of embryonic origin - high dose chemotherapy followed by rescue with stem cells becomes a reasonable option to avoid neurocognitive and endocrinological sequelae radiation induced⁽⁸⁻⁹⁾

Choroid plexus carcinoma has only small published series, the main publication being the Head Start sequential studies in which it showed benefit. Particularly TP53 and R337H mutations should be investigated before indicated TCTH⁽¹⁰⁾.

High-grade gliomas in first remission have been the subject of studies, which have not been reproduced

later. Patients undergoing surgeries with total or subtotal resection had better results⁽¹¹⁾.

Ependymomas seem not to have benefited from the use of autologous transplants^(12,13).

Brainstem gliomas are also tumors with poor results and autologous transplantation did not achieve the desired effect⁽¹⁴⁾.

In the few CNS germinal tumors, autologous transplantation are explored in the management of patients with recurrent or refractory neoplasms and could be indicated in this population^(15,16)

RETINOBLASTOMA

Retinoblastoma (RB) is a rare embryonic tumor that originates in the neural retina, being the most frequent intraocular malignant tumor in children. More than 90% of cases are diagnosed before the age of five (median 2 years)⁽¹⁷⁾.

The manifestation of the disease can be unilateral or bilateral, the latter being related to germline mutations. While intraocular RB has an excellent survival rate, patients with extraocular RB have historically a worse prognosis.⁽¹⁸⁾

Many groups have noted that intensified treatment in patients with advanced or metastatic disease with high doses of chemotherapy and autologous stem cell rescue (ASCT) has been associated with improved survival. (19,20,21) It is possible to achieve tumor control in those patients with trilateral, advanced bilateral disease, without CNS metastasis, and in those with tumor on the surgical margin of the optic nerve and / or extra-scleral extension.⁽¹⁷⁾

The prospective, multicenter and international study carried out by COG (ARET0321) evaluated the use of high-dose chemotherapy, using carboplatin, etoposide and thiotepa, with ASCT, in patients with advanced disease. Event-free survival (EFS) at 36 months was 87.7% (stages 2 and 3); 79.3% (4a); 8% (4b / trilateral disease). The observed results significantly improved EFS in each subgroup compared to historical results, especially for patients with extraocular and metastatic disease without CNS involvement⁽⁴⁾.

TABLE 1 – Indications for transplantation in pediatric solid tumors

Disease	Autologous	Allogeneic	Comments
Retinoblastoma - extra ocular disease	CI	NR	
Retinoblastoma Relapse	CI	NR	
Pineoblastoma (trilateral retinoblastoma)	CI	NR	
Teratoid rhabdoid tumors	CI	NR	
Medulloblastoma younger than four years old (except low risk groups)	CI	NR	Unfavorable histology and molecular profile
Medulloblastoma relapse	CI	NR	Just special cases without previous radiotherapy
Central Nervous system Germ Cell tumor	CI	NR	
Glioblastoma multiforme	CO	NR	
Ependimoma	NR	NR	
High grade Gliomas	CO	NR	
Brainstem gliomas	NR	NR	
Choroid plexus carcinoma	CI	NR	Search for R337H and P53 mutations

Legends: Clinically indicated (CI) Clinical option (OC) - Generally not recommended (NR)

REFERENCES

- 1 - Chi SN, Gardner SL, Levy AS, et al .: Feasibility and response to induction chemotherapy intensified with high- methotrexate dose for young children with newly diagnosed high-risk disseminated medulloblastoma. *J Clin Oncol.* 2004;22(24):4881-7.
- 2 - Dhall G, Grodman H, Ji L, et al . Outcome of children less than three years old at diagnosis with non-metastatic medulloblastoma treated with chemotherapy on the “ Head Start “I and II protocols. *Pediatr Blood Cancer.*2008;50(6):1 169-75.
3. Bergthold G, El Kababri M, Varlet P, et al. High-dose bu-thiotepa followed by posterior fossa RT in young children with classical or incompletely resected medulloblastoma. *Pediatr Blood Cancer.* 2014;61(5):907-12
4. Butturini AM, Jacob M, Aguajo J, et al. High-dose chemotherapy and autologous hematopoietic progenitor cell rescue in children with recurrent medulloblastoma and supratentorial primitive neuroectodermal tumors: the impact of prior radiotherapy on outcome. *Cancer.* 2009;115(13):2956-63.
5. Gilheeny SW, Khakoo Y, Souweidane M, et al. Thiotepa / topotecan / carboplatin with autologous stem cell rescue in recurrent / refractory / poor prognosis pediatric malignancies of the central nervous system. *Pediatr Blood Cancer.*2010;54(4) 591-5.
6. Osorio DS, Dunkel IJ, Cervone KA, et al. Tandem thiotepa with autologous hematopoietic cell rescue in patients with recurrent, refractory, or poor prognosis solid tumor malignancies. *Pediatr Blood Cancer.* 2018;65(1): 10.1002/pbc.26776.
7. Butturini AM, Jacob M, Aguajo J, et al. High-dose chemotherapy and autologous hematopoietic progenitor cell rescue in children with recurrent medulloblastoma and supratentorial primitive neuroectodermal tumors. *Cancer.* 2009;115(13):2956-2963.

8. Zaky W, Dhall G, Ji L, et al. Intensive induction chemotherapy followed by myeloablative chemotherapy with autologous hematopoietic progenitor cell rescue for young children newly-diagnosed with central nervous system atypical teratoid / rhabdoid tumors: the Head Start III experience. *Pediatr Blood Cancer*. 2014;61(1):95-101.
9. Biswas A, Kashyap L, Kakkar A, et al. Atypical teratoid / rhabdoid tumors: challenges and search for solutions. *Cancer Manag Res*. 2016;8:115-125.
10. Zaky W, Dhall G, Khatua S, et al. Choroid plexus carcinoma in children: the Head Start experience. *Pediatr Blood Cancer*. 2015;62(5):784-9.
11. Baek HJ, Park HJ, Sung KW, et al. Myeloablative chemotherapy and autologous stem cell transplantation in patients with relapsed or progressed central nervous system germ cell tumors: results of Korean Society of Pediatric Neuro-Oncology (KSPNO) S-053 study. *J Neurooncol*. 2013;114(3):329-38
12. Finlay JL, Dhall G, Boyett JM, et al. Children's Cancer Group. Myeloablative chemotherapy with autologous bone marrow rescue in children and adolescents with recurrent malignant astrocytoma: outcome compared with conventional chemotherapy: a report from the Children's Oncology Group. *Pediatr Blood Cancer*. 2008;51(6):806-11.
13. Zacharoulis S, Levy A, Chi SN, et al. Outcome for young children newly diagnosed with ependymoma, treated with intensive induction chemotherapy followed by myeloablative chemotherapy and autologous stem cell rescue. *Pediatr Blood Cancer*. 2007;49(1):34-40.
14. Venkatramani R, Ji L, Lasky J, et al. Outcome of infants and young children with newly diagnosed ependymoma treated on the "Head Start" III prospective clinical trial. *J Neurooncol*. 2013;113(2):285-91.
15. Baek HJ, Park HJ, Sung KW. Myeloablative chemotherapy and autologous stem cell transplantation in patients with relapsed or progressed central nervous system germ cell tumors: results of Korean Society of Pediatric Neuro-Oncology (KSPNO) S-053 study. *J Neurooncol*. 2013;114(3):329-38
16. Modak S, Gardner S, Dunkel IJ, et al. Thiopeta-based high-dose chemotherapy with autologous stem-cell rescue in patients with recurrent or progressive CNS germ cell tumors. *J Clin Oncol*. 2004;22(10):1934-43.
17. Jaradat I, Mubiden R, Salem A, et al. High-dose chemotherapy followed by stem cell transplantation in the management of retinoblastoma: a systematic review. *Hematol Oncol Stem Cell Ther* 2012;5(2):107-17.
18. Antoneli CB, Ribeiro KB, Rodriguez-Galindo C, et al. The addition of ifosfamide/etoposide to cisplatin/teniposide improves the survival of children with retinoblastoma and orbital involvement. *J Pediatr Hematol Oncol*. 2007;29(10):700-4.
19. Dunkel IJ, Chan HS, Jubran R, et al. High-dose chemotherapy with autologous hematopoietic stem cell rescue for stage 4B retinoblastoma. *Pediatr Blood Cancer*. 2010;55(1):149-52
20. Lee SH, Yoo KH, Sung KW, et al. Tandem high-dose chemotherapy and autologous stem cell rescue in children with bilateral advanced retinoblastoma. *Bone Marrow Transplant*. 2008;42(6):385-91
21. Dunkel IJ, Krailo MD, Chantada GL, et al. Intensive multi-modality therapy for extraocular retinoblastoma (RB): A Children's Oncology Group (COG) trial (ARET0321). *J Clin Oncol*. 2017;35(15 suppl):10506.