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

Paulo Henrique dos Santos Klinger MD1,2, Karoline Helena Silva da Silva MD3, Patrícia Shimoda Ikeuti MD3, Lauro José Gregorian MD, PhD4,5, Mariana Bohns Michalowski MD PhD4,5, Gabriele Zamperlini Netto MD6,7, Carla Nolasco Monteiro Breviglieri MD2,6, Fernanda Lima Lelis MD8,9, Natália Maria Tavares Ferreira Borges MD8,9, Simone de Castro Resende Franco MD10, Cláudio Galvão de Castro Junior MD, MsC11,12

1) Laboratório de Investigação Médica em Patogênese e Terapia dirigida em Onc-Imuno-Hematologia (LIM-31), Departamento de Hematologia, Hospital das Clínicas HCFMUSP, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil
2) Hospital Samaritano – São Paulo – SP
3) Instituto de Oncologia Pediátrica – GRAACC – UNIFESP – São Paulo – SP
4) Hospital de Clínicas de Porto Alegre – Porto Alegre – RS
5) Departamento de Pediatria – Universidade Federal do Rio Grande do Sul – Porto Alegre – RS
6) Instituto do Tratamento do Câncer Infantil ITACI – Hospital das Clínicas – Universidade de São Paulo – São Paulo – SP
7) Hospital Israelita Albert Einstein – São Paulo – SP
8) Hospital Martagão Gesteira – Salvador – BA
9) Hospital São Rafael – Salvador – BA
10) Hospital da Criança de Brasília – Brasília – DF
11) Hemomed Instituto de Oncologia e Hematologia – São Paulo – SP
12) Hospital São Camilo – São Paulo – SP

Correspondence to: claudio.junior1967@gmail.com

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 (46).
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)

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