High-dose chemotherapy followed by stem cell transplantation in the management of retinoblastoma: a systematic review

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BACKGROUND AND OBJECTIVES: In recent years, there has been an increasing role for stem cell transplantation in the management of retinoblastoma. The aim of this study was to systematically review the role high-dose chemotherapy followed by stem cell transplantation in the treatment of patients with metastatic or relapsed, trilateral or bilateral advanced retinoblastoma, and in patients with tumor at the surgical margin of the optic nerve and/or extrascleral extension.

DESIGN: Systematic literature review.

METHODS: We performed an extensive PubMed database search on 25 February 2012 for studies describing the use of high-dose chemotherapy followed by stem cell transplantation in the management of patients with retinoblastoma.

RESULTS: We located 15 studies that met the inclusion criteria and that included 101 patients. Following treatment for metastatic and relapsed disease, 44 of 77 patients (57.1%) were alive with no evidence of disease at the time of follow-up. However, a higher rate of local relapse developed in patients with CNS metastases (73.1%), which dropped to 47.1% in patients who received thiotepa. In patients with trilateral or bilateral advanced retinoblastoma, 5 of 7 (71.4%) with reported outcome data were alive with no evidence of disease at the time of follow-up. In patients with tumor at the surgical margin of the optic nerve and/or extrascleral extension, 6 of 7 patients (85.7%) were alive with no evidence of disease at the time of follow-up.

CONCLUSIONS: Durable tumor control is possible in patients with non-CNS metastases, trilateral or bilateral advanced retinoblastoma, and in patients with tumor at the surgical margin of the optic nerve and/or extrascleral extension. Patients with CNS metastases require thiotepa to improve tumor control.

Retinoblastoma is the most common intraocular malignancy in childhood. In developed countries, most patients present with confined, intraocular disease. Secondary to late presentation, advanced retinoblastoma (locally advanced and metastatic disease) is more common in developing countries and is associated with exceedingly poor prognosis. In these cases, response to conventional therapies (enucleation, external-beam radiotherapy, and chemotherapy) has been poor. Several groups have proposed the use of high-dose chemotherapy in these patients; however, only a limited number of studies have addressed the role of high-dose chemotherapy followed by stem cell transplantation in the treatment of patients with metastatic or relapsed, trilateral or bilateral advanced retinoblastoma, and for patients with tumor at the surgical margin of the optic nerve and/or extrascleral extension. The aim of this study was to systematically review and investigate the current role of stem cell transplantation in the management of retinoblastoma.

METHODS
A comprehensive PubMed search was conducted on 25 February 2012. The following search terms were used: "retinoblastoma", "chemotherapy", "high-dose", "stem cell" and "transplant". No restrictions were applied to
systematic review

the date of publication; however, this search was limited
to papers in English. Reports describing the utilization
of high-dose chemotherapy followed by stem cell trans-
plantation in the management of patients with retino-
blastoma were considered. Studies addressing the role
of chemotherapy were excluded if no direct mention
was made to the rescue of the bone marrow with subse-
quent stem cell transplantation. Furthermore, reference
lists of included studies were hand-searched to identify
relevant missing publications. Articles were assessed
and selected for inclusion by all authors. Full text ar-
ticles of eligible abstracts were reviewed. Only original
studies were included. Data pertaining to date of publi-
cation, study design and period, country of origin, num-
ber of patients, indication for treatment, chemotherapy
regimen, therapeutic outcomes and associated toxicity
were extracted using a predefined datasheet. Adequate
high-dose chemotherapy regimens were defined as
does as those consisting of a platinum agent and an alkylating
compound in addition to etoposide.\textsuperscript{17} Due to its excel-
 lent CNS penetration, the impact of thiopeta on the
incidence of CNS relapse in patients with metastatic
retinoblastoma was evaluated.\textsuperscript{18}

results

The preliminary search yielded 53 abstracts. Three non-
English publications were excluded. Of the remaining
50 studies, 20 were excluded following the first screen
of the title and abstract. Thirty full-text articles were
retrieved for detailed evaluation of which 17 were in-
eligible (did not address the use of high-dose chemo-
therapy followed by stem cell transplantation (n=16)
or reported overlapping patient populations (n=1). Addition-
ally, 2 papers were identified from the refer-
ce lists of included reports. Overall, 15 studies, which
include 101 patients, met the inclusion criteria and
formed the basis of this systematic review (Figure 1).
The analysis involved 77 patients with metastatic or re-
lapsed retinoblastoma (13 articles; Table 1), 17 patients
with trilateral or bilateral advanced retinoblastoma (3
articles; Table 2), and 7 patients with tumor at the
surgical margin of the optic nerve and/or extrascleral
extension (2 articles; Table 3). Since most studies were
retrospective in nature and reported on a heterogenous
group of patients, strict inclusion and exclusion criteria
could not be assessed.

Secondary to the poor overall prognosis of reti-
oblastoma cases with CNS metastases, we opted to
classify metastatic retinoblastoma patients into those
presenting with or without CNS disease. Of a total of
77 included patients, 26 and 43 patients presented with
CNS and non-CNS metastases, respectively, while
only 8 patients in this group harbored isolated orbital
relapse.\textsuperscript{2-14} Of 69 patients who received high-dose che-
motherapy, 53 patients (76.8\%) received an adequate
chemotherapy combination. Treatment-associated
morbidity data were available in 7 reports and con-
sisted mainly of grade IV hematological and gastroin-
testinal toxicity.\textsuperscript{3,4,7,8,11-13} One patient died secondary to
this intensive chemotherapy protocol.\textsuperscript{9} Overall, 44 pa-
tients (57.1\%) were alive with no evidence of disease
at the time of follow-up. Treatment outcome was not
as good in patients presenting with CNS metastases
where 19 of 26 patients (73.1\%) eventually developed
CNS relapse, probably secondary to the use of inap-
propriate chemotherapeutic regimens (associated with
poor CNS penetration); only 8 of 17 (47.1\%) patients
who received thiopeta subsequently developed CNS
relapse.\textsuperscript{2,14}

Eight patients had trilateral retinoblastoma while
9 harbored bilateral advanced disease.\textsuperscript{10,15,16} Lee et al\textsuperscript{16}
reported neutropenic fever and hepatic veno-occlusive
disease in 9 of 9 and 2 of 9 patients, respectively. In ad-
dition, Dunkel and colleagues\textsuperscript{10} reported on 1 patient
who died due to sepsis and multi-organ system
failure secondary to chemotherapy. Overall, 5 of the 7
patients (71.4\%) with reported outcome data were alive
with no evidence of disease at the time of follow-up.\textsuperscript{10,15}

Seven patients with tumors at the surgical margin
of the optic nerve and/or extrascleral extension were
recovered with high-dose chemotherapy followed by stem
cell transplantation.\textsuperscript{2,4} Kremens et al\textsuperscript{4} reported grade IV
gastrointestinal treatment-related toxicity; however, no
treatment-related mortality was reported. Overall, 6 of
7 patients (85.7\%) were alive with no evidence of dis-
case at the time of follow-up.\textsuperscript{2,4}

discussion

This study represents the first detailed systematic re-
view addressing the role of high-dose chemotherapy
followed by stem cell transplantation in retinoblastoma.
Unfortunately, most of the included studies were small
retrospective case series (n=9)\textsuperscript{2-4,A,8,10,12,3,16} or single case
reports (n=5).\textsuperscript{5,7,9,11,14} There was only one prospective
report that addressed the use of stem cell transplant in
pediatric malignancies in general and included 1
patient with trilateral retinoblastoma.\textsuperscript{15} In addition,
most of the reviewed reports originated from developed
countries (n=12).\textsuperscript{2,4,A,11,16} According to our review, the
use of high-dose chemotherapy followed by stem cell
transplantation in retinoblastoma patients was first
proposed by Matsubara et al\textsuperscript{8} in 1986. Since then, this
treatment regimen has been expanded to include pa-
tients with tumors at the surgical margin of the optic
nerve and/or extrascleral extension (first patient treated in 1989)\(^2\) and trilateral retinoblastoma (first patient treated in 1997).\(^10\)

The treatment protocol in the majority of included studies consisted of induction poly-chemotherapy (with the aim of achieving partial or complete tumor response) followed by high-dose chemotherapy and autologous stem cell transplantation. Only one case report narrated the performance of allogeneic stem cell transplantation using an identical HLA-matched sibling.\(^3\) In conjunction with high-dose chemotherapy, external-beam irradiation (for bulky, metastatic sites) has been reported 7 studies\(^2,3,6,8,10,12,13\) while intra-thecal chemotherapy and radio-immunotherapy were reported in 4 studies.\(^5,6,8,10\) On the other hand, prophylactic cranial irradiation was less commonly prescribed. However, due to the non-randomized nature of the included studies and the variability of treatment protocols among patients in each study, we cannot accurately account for the impact of individual treatments on the outcome of these patients.

Thirteen studies addressed the role of high-dose chemotherapy followed by stem cell transplantation in patients with metastatic and relapsed retinoblastoma.\(^2-14\) Although metastatic retinoblastoma is more common in developing countries (secondary to late patient presentation/diagnosis and lack of adequate healthcare facilities), only 3 reports originated from developing countries (including a case series jointly reported with a US institution).\(^3,9,10\) Possible explanations for the lack of relevant publications from developing counties include publication bias, reluctance to implement such novel, technically-demanding, non-evidence-based practices (stem cell transplantation) and the unbalanced physical distribution of care providers. Currently, the Children’s Oncology Group (COG) is undertaking a promising international study (COG ARET 0321) that aims at defining the most appropriate treatment strategy for patients with extraocular retinoblastoma.\(^19\) Results of this study are set to improve therapeutic outcomes for advanced retinoblastoma patients in developing countries. Overall, according to our review, treatment-related toxicity was as expected from a myeloablative high-dose chemotherapy regimen (grade IV myelosuppression and gastrointestinal toxicity) while treatment-associated mortality was rarely reported—only 1 of 77 patients (1.3%). The length of follow-up greatly varied between the included studies (from 2 to 103 months); however, this strategy achieved durable tumor control in approximately 60% of patients. Outcome appears to vary according to location of metastatic spread; patients with non-CNS metastases fair better than those with CNS disease. This is possibly secondary to the poor CNS penetration of conventional chemotherapeutic agents; only 47.1% of patients who received thiotepa subsequently developed CNS relapse. Overall, the outcome of patients with metastatic and relapsed retinoblastoma treated by high-dose chemotherapy followed by stem cell transplantation appears to be superior to historical controls treated by conventional chemotherapy.\(^8\)

Three studies addressed the role of high-dose chemotherapy followed by stem cell transplantation in patients with trilateral or bilateral advanced retinoblastoma.\(^10,15,16\) Due to the small number of included cases (17 patients), accurate assessment of the safety of this therapeutic regimen was not possible; however, the reported morbidity/ mortality were within expectations (grade IV myelosuppression and 1 case of treatment-related toxicity was as expected from a myeloablative high-dose chemotherapy regimen (grade IV myelosuppression and gastrointestinal toxicity) while treatment-associated mortality was rarely reported—only 1 of 77 patients (1.3%). The length of follow-up greatly varied between the included studies (from 2 to 103 months); however, this strategy achieved durable tumor control in approximately 60% of patients. Outcome appears to vary according to location of metastatic spread; patients with non-CNS metastases fair better than those with CNS disease. This is possibly secondary to the poor CNS penetration of conventional chemotherapeutic agents; only 47.1% of patients who received thiotepa subsequently developed CNS relapse. Overall, the outcome of patients with metastatic and relapsed retinoblastoma treated by high-dose chemotherapy followed by stem cell transplantation appears to be superior to historical controls treated by conventional chemotherapy.\(^8\)

Three studies addressed the role of high-dose chemotherapy followed by stem cell transplantation in patients with trilateral or bilateral advanced retinoblastoma.\(^10,15,16\) Due to the small number of included cases (17 patients), accurate assessment of the safety of this therapeutic regimen was not possible; however, the reported morbidity/ mortality were within expectations (grade IV myelosuppression and 1 case of treatment-related toxicity was as expected from a myeloablative high-dose chemotherapy regimen (grade IV myelosuppression and gastrointestinal toxicity) while treatment-associated mortality was rarely reported—only 1 of 77 patients (1.3%). The length of follow-up greatly varied between the included studies (from 2 to 103 months); however, this strategy achieved durable tumor control in approximately 60% of patients. Outcome appears to vary according to location of metastatic spread; patients with non-CNS metastases fair better than those with CNS disease. This is possibly secondary to the poor CNS penetration of conventional chemotherapeutic agents; only 47.1% of patients who received thiotepa subsequently developed CNS relapse. Overall, the outcome of patients with metastatic and relapsed retinoblastoma treated by high-dose chemotherapy followed by stem cell transplantation appears to be superior to historical controls treated by conventional chemotherapy.\(^8\)
Table 1. Characteristics and outcome for patients who underwent high-dose chemotherapy and peripheral blood stem cell transplant for metastatic or relapsed retinoblastoma.

<table>
<thead>
<tr>
<th>Study/data published</th>
<th>Study design</th>
<th>Study period</th>
<th>Country of origin</th>
<th>Total number of patients</th>
<th>Number of patients with isolated relapse</th>
<th>Number of patients with CNS: non-CNS metastases</th>
<th>Response to induction CTX</th>
<th>High-dose chemotherapy</th>
<th>Adequate high-dose CTX regimen used?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Namouni et al² 1997</td>
<td>Retrospective</td>
<td>1989-1994</td>
<td>France</td>
<td>19</td>
<td>7</td>
<td>4:8</td>
<td>- 11 patients; complete response</td>
<td>CEC</td>
<td>Yes</td>
</tr>
<tr>
<td>Palma et al² 2011</td>
<td>Retrospective</td>
<td>2002-2008</td>
<td>3 centers in South America</td>
<td>11</td>
<td>None</td>
<td>4:7</td>
<td>- 6 patients; CTE</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Kremens et al² 2003</td>
<td>Retrospective</td>
<td>1992-2001</td>
<td>Germany</td>
<td>4</td>
<td>None</td>
<td>0:4</td>
<td>- 3 patients; CTE</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Tsuruta et al ² 2011</td>
<td>Case report</td>
<td>NA</td>
<td>Japan</td>
<td>1</td>
<td>None</td>
<td>1:0</td>
<td>Complete response</td>
<td>TM</td>
<td>No (platinum agent not used)</td>
</tr>
<tr>
<td>Dunkel et al ² 2010</td>
<td>Retrospective</td>
<td>2000-2006</td>
<td>USA</td>
<td>8</td>
<td>1</td>
<td>7:0</td>
<td>All patients achieved major/complete response</td>
<td>- 2 patients; CTE</td>
<td>4/5c</td>
</tr>
<tr>
<td>Hertzberg et al ² 2001</td>
<td>Case report</td>
<td>NA</td>
<td>Germany</td>
<td>1</td>
<td>None</td>
<td>0:1</td>
<td>Complete response</td>
<td>CTE</td>
<td>Yes</td>
</tr>
</tbody>
</table>

¹Study included patients with involved cut end of optic nerve/extrasclear extension and patients presenting with disease relapse/distant metastases
²These patients were treated after publication of the first report by the same authors
³Only 5 patients received high-dose chemotherapy
⁴One of these patients also received IT radiotimmunotherapy
### Table 1 cont. Characteristics and outcome for patients who underwent high-dose chemotherapy and peripheral blood stem cell transplant for metastatic or relapsed retinoblastoma.

<table>
<thead>
<tr>
<th>Study/date published</th>
<th>Type of HSC</th>
<th>Other treatments in addition to transplant</th>
<th>Median follow-up period in months (range)</th>
<th>Toxicity (number of patients affected/total number of patients)</th>
<th>Treatment related mortality</th>
<th>Survival at last follow-up</th>
<th>Patterns of failure in patients with CNS metastases</th>
<th>CNS relapse following thiopeta</th>
<th>Second malignancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Namouni et al 1997</td>
<td>Auto in all patients</td>
<td>EBRT in 12 patients (all CNS metastases patients received EBRT)</td>
<td>27 (5-74)</td>
<td>Not clear*</td>
<td>None</td>
<td>- 12 patients were alive NED</td>
<td>3/4 patients had relapse in the CNS and DDTD</td>
<td>NA (none received thiopeta)</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Palma et al 2011</td>
<td>Auto in all patients</td>
<td>Cranial EBRT for 3 patients with CNS metastases</td>
<td>39 (27-56)</td>
<td>No non-hematological grade IV toxicity</td>
<td>None</td>
<td>7 patients alive NED</td>
<td>- 2/4 patients had relapse in the CNS and DDTD</td>
<td>2/4</td>
<td>None</td>
</tr>
<tr>
<td>Kremens et al 2003</td>
<td>Auto in all patients</td>
<td>IT MTX in the patient who developed leptomeningal relapse</td>
<td>33.5 (9-107)</td>
<td>Grade III and IV GI toxicity in 4/5</td>
<td>None</td>
<td>4 patients were alive NED (1 patient developed leptomeningal relapse but was salvaged)</td>
<td>NA</td>
<td>0/3</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Tsuruta et al 2011</td>
<td>Allo</td>
<td>High-dose Busulfan and 2nd HSCT followed by IT thiopeta and cytosine arabinoside followed by 3rd PBSC transplant due to additional relapse</td>
<td>2 [NA]</td>
<td>Not mentioned</td>
<td>None</td>
<td>DDTD 2 months after last HSCT</td>
<td>The patient had relapse in the CNS</td>
<td>1/1</td>
<td>None</td>
</tr>
<tr>
<td>Dunkel et al 2010</td>
<td>Auto</td>
<td>- 2 patients; CSI - 2 patients; focal EBRT*</td>
<td>12 (3-101)</td>
<td>Not mentioned</td>
<td>One patient died of toxicity while receiving induction CTX</td>
<td>- 5 patients DDTD - 2 patients; alive NED</td>
<td>5/7 patients had CNS relapse</td>
<td>2/3</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Hertzberg et al 2001</td>
<td>Auto</td>
<td>None</td>
<td>48 (NA)</td>
<td>Late toxicity; hypergonadotropic hypogonadism</td>
<td>None</td>
<td>Alive NED</td>
<td>NA</td>
<td>0/1</td>
<td>None</td>
</tr>
</tbody>
</table>

*Study included patients with involved cut end of optic nerve/extrasclear extension and patients presenting with disease relapse/distant metastases

*These patients were treated after publication of the first report by the same authors

*Only 5 patients received high-dose chemotherapy

*One of these patients also received IT radioimmunotherapy
Table 1 cont. Characteristics and outcome for patients who underwent high-dose chemotherapy and peripheral blood stem cell transplant for metastatic or relapsed retinoblastoma.

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<tr>
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<th>Study period</th>
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<th>High dose chemotherapy</th>
<th>Adequate high-dose CTX regimen used?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matsubara et al8 2005</td>
<td>Retrospective</td>
<td>1986-2000</td>
<td>Japan</td>
<td>5</td>
<td>None</td>
<td>2:3</td>
<td>All patients achieved complete response</td>
<td>CyMP, MEC, CyTM</td>
<td>Yes</td>
</tr>
<tr>
<td>Chantada et al9 2010</td>
<td>Case report</td>
<td>2002-2008</td>
<td>Argentina</td>
<td>1*</td>
<td>None</td>
<td>1:0</td>
<td>Complete response</td>
<td>CEC</td>
<td>Yes</td>
</tr>
<tr>
<td>Dunkel et al10 2010</td>
<td>Retrospective</td>
<td>1997-2005</td>
<td>USA, Argentina</td>
<td>6</td>
<td>None</td>
<td>6:0</td>
<td>Not mentioned</td>
<td>CT, CyM, CyTM</td>
<td>1/3f</td>
</tr>
<tr>
<td>Dimaras et al11 2009</td>
<td>Case report</td>
<td>NA</td>
<td>Canada</td>
<td>1</td>
<td>None</td>
<td>1:0</td>
<td>Complete response</td>
<td>CEC</td>
<td>Yes</td>
</tr>
<tr>
<td>Dunkel et al12 2010</td>
<td>Retrospective</td>
<td>1993-2006</td>
<td>USA</td>
<td>15</td>
<td>None</td>
<td>0:15</td>
<td>All patients achieved complete response</td>
<td>CT, CT, CT, CyM</td>
<td>5/13g</td>
</tr>
</tbody>
</table>

*There was 1 patient who received high-dose chemotherapy followed-by HSCT in this prospective study
†Only 3 patients received high-dose chemotherapy
‡Only 13 patients received high-dose chemotherapy
Table 1 cont. Characteristics and outcome for patients who underwent high-dose chemotherapy and peripheral blood stem cell transplant for metastatic or relapsed retinoblastoma.

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<tr>
<td>Matsubara et al. 2005</td>
<td>Auto in all patients</td>
<td>- 1T MTX in all patients - 4/5 patients received EBRT to bulky sites - 2/2 patients with CNS metastases received cranial irradiation</td>
<td>48 (4-113)</td>
<td>- All patients; grade IV mucositis - 1 patient; elevated liver enzymes</td>
<td>None</td>
<td>- 3 patients; alive NED - 2 patients; DDTC</td>
<td>2/2 patients had CNS relapse</td>
<td>0/1</td>
<td>None</td>
</tr>
<tr>
<td>Chantada et al. 2010</td>
<td>Auto</td>
<td>None</td>
<td>5 (NA)</td>
<td>Not mentioned</td>
<td>Not mentioned</td>
<td>This patient had relapse DDTD 5 months after HSCT</td>
<td>The patient had relapse in the CNS</td>
<td>This patient did not receive thiotepa</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Dunkel et al. 2010</td>
<td>Auto in all patients</td>
<td>- 2 patients; EBRT (site not specified) - 1 patient; radio-immunotherapy</td>
<td>17 (5-36)</td>
<td>NA</td>
<td>None</td>
<td>- 5 patients; DDTD - 1 patient; alive NED</td>
<td>5/6 patients had CNS relapse</td>
<td>1/2</td>
<td>NA</td>
</tr>
<tr>
<td>Dimaras et al. 2009</td>
<td>Auto</td>
<td>Periodic intraventricular topotecan and cytarabine</td>
<td>100 (NA)</td>
<td>Grade IV myelotoxicity</td>
<td>None</td>
<td>Alive NED</td>
<td>0/1</td>
<td>This patient did not receive thiotepa</td>
<td>None</td>
</tr>
<tr>
<td>Dunkel et al. 2010</td>
<td>Auto in all patients</td>
<td>- 7 patients; EBRT to bulky sites</td>
<td>103 (34-202) in alive NED patients</td>
<td>Grade IV myelotoxicity in most patients</td>
<td>None</td>
<td>- 10 patients; alive NED - 5 patients; DDTD</td>
<td>NA (None had CNS metastases)</td>
<td>2/2</td>
<td>- 3 patients; osteosarcoma</td>
</tr>
</tbody>
</table>
### Table 1 cont. Characteristics and outcome for patients who underwent high-dose chemotherapy and peripheral blood stem cell transplant for metastatic or relapsed retinoblastoma.

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<th>Response to induction CTX</th>
<th>High dose chemotherapy</th>
<th>Adequate high-dose CTX regimen used?</th>
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<tbody>
<tr>
<td>Rodriguez-Galindo et al13 2003</td>
<td>Retrospective</td>
<td>NA</td>
<td>USA</td>
<td>4</td>
<td>None</td>
<td>0:4</td>
<td>All patients achieved complete response</td>
<td>- 1 patient; CE</td>
<td>Yes</td>
</tr>
<tr>
<td>Yamane et al14 1999</td>
<td>Case report</td>
<td>HSCT done in 1994</td>
<td>Japan</td>
<td>1</td>
<td>None</td>
<td>0:1</td>
<td>Partial response</td>
<td>- 1 patient; Cy and topotecan</td>
<td>No</td>
</tr>
</tbody>
</table>

Study/date published: Study design: Study period: Country of origin: Total number of patients: Number of patients with isolated relapse: Number of patients with CNS: non-CNS metastases: Response to induction CTX: High dose chemotherapy: Adequate high-dose CTX regimen used?

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<tbody>
<tr>
<td>Rodriguez-Galindo et al13 2003</td>
<td>Auto in all patients</td>
<td>All patients received EBRT to sites of bone metastases</td>
<td>78 (44-88)</td>
<td>1 patient developed fungal sepsis</td>
<td>None</td>
<td>- 2 patients; alive NED</td>
<td>NA (None had CNS metastases)</td>
<td>None</td>
<td>NA</td>
</tr>
<tr>
<td>Yamane et al14 1999</td>
<td>Auto</td>
<td>None</td>
<td>48 (NA)</td>
<td>NA</td>
<td>None</td>
<td>Alive NED</td>
<td>NA (None had CNS metastases)</td>
<td>NA</td>
<td>None</td>
</tr>
</tbody>
</table>

**CTX**: Carboplatin, thiopeta, etoposide; EBRT: External-beam radiation therapy; CEC: Cyclophosphamide, etoposide, carboplatin; MEC: Melphalan, etoposide, carboplatin; TM: Thiopeta, melphalan; PBSC: Peripheral blood stem cell transplantation; IT: Intrathecal; NED: No evidence of disease; CNS: Central nervous system; DDIT: Dead due to disease; PD: Progressive disease; GI: Gastrointestinal toxicity; CSI: Cranio-spinal irradiation; CyMP: Cyclophosphamide, melphalan, cisplatin; CyTM: Cyclophosphamide, thiopeta, melphalan; CyM: Cyclophosphamide, melphalan; CSF: Cerebrospinal fluid; CyT: Cyclophosphamide, thiopeta; MTX: Methotrexate
Table 2. Characteristics and outcome for patients who underwent high-dose chemotherapy and peripheral blood stem cell transplant for trilateral and bilateral advanced retinoblastoma

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>Study period</th>
<th>Country of origin</th>
<th>Number of patients</th>
<th>Indication</th>
<th>Response to induction CTX</th>
<th>High dose chemotherapy</th>
<th>Adequate high-dose CTX regimen used?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dunkel et al10</td>
<td>Retrospective</td>
<td>1997-2005</td>
<td>USA, Argentina</td>
<td>7</td>
<td>Trilateral disease</td>
<td>Not mentioned</td>
<td>- 2 patients; CT - 1 patient; CT - 1 patient; CT and topotecan - 1 patient; CyM</td>
<td>2/6*</td>
</tr>
<tr>
<td>Giheeney et al15</td>
<td>Prospective</td>
<td>NA</td>
<td>USA</td>
<td>1</td>
<td>Trilateral disease</td>
<td>Not mentioned</td>
<td>CT and topotecan</td>
<td>0/1</td>
</tr>
<tr>
<td>Lee et al16</td>
<td>Retrospective</td>
<td>2001-2006</td>
<td>South Korea</td>
<td>9</td>
<td>Bilateral advanced disease</td>
<td>- 6 patients; PR - 3 patients; SD</td>
<td>5 patients; CTE - 4 patients; MEC</td>
<td>9/9</td>
</tr>
</tbody>
</table>

*Only 6 patients received high-dose chemotherapy

Table 2 cont. Characteristics and outcome for patients who underwent high-dose chemotherapy and peripheral blood stem cell transplant for trilateral and bilateral advanced retinoblastoma

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of HSCT</th>
<th>Other treatments in addition to transplant</th>
<th>Enucleation</th>
<th>Median follow-up period in months (range)</th>
<th>Toxicity (number of patients affected/total number of patients)</th>
<th>Treatment related mortality</th>
<th>Functional eye preservation</th>
<th>Survival</th>
<th>Second malignancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dunkel et al10</td>
<td>Auto in all patients</td>
<td>- 1 patient received EBT - 1 patient received IT topotecan</td>
<td>None</td>
<td>76 (3-104)</td>
<td>Neutropenic fever: 9/9 Hepatic VOD: 2/9</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Giheeney et al15</td>
<td>Auto</td>
<td>Gross tumor resection after transplant</td>
<td>Yes, post</td>
<td>59 (NA)</td>
<td>Neutropenic fever: 9/9 Hepatic VOD: 2/9</td>
<td>NA</td>
<td>NA</td>
<td>Alive NED</td>
<td>None</td>
</tr>
<tr>
<td>Lee et al16</td>
<td>Auto in all patients</td>
<td>Local therapy in at least one eye in 8 patients</td>
<td>Yes, post transplant in 5 patients (5 eyes)</td>
<td>42 (22-82)</td>
<td>Neutropenic fever: 9/9 Hepatic VOD: 2/9</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>None</td>
</tr>
</tbody>
</table>

CTE: Carboplatin, thiotepa, etoposide; CyTE: Cyclophosphamide, thiotepa, etoposide; CyM: Cyclophosphamide, melphalan; EBT: External-beam radiation therapy; MEC: Melphalan, etoposide, carboplatin; VOD: Veno-occlusive disease; PR: Partial response; SD: Stable disease
related death). Nonetheless, therapeutic outcome in these patients was superior to those presenting with metastatic disease (5 of the 7 evaluable patients [71.4%] were alive with no evidence of disease at the time of follow-up).

Two studies addressed the role of high-dose chemotherapy followed by stem cell transplantation in patients with tumor at the surgical margin of the optic nerve and/or extrascleral extension.\(^2,^4\) In these patients, treatment-related toxicity was within expectations while excellent outcome was achieved (6 of 7 patients were alive with no evidence of disease at the time of follow-up). Traditionally, these patients were offered external-beam radiotherapy; however, this is associated with significant side effects. Several studies have reported the occurrence of second malignancy following radiation therapy in retinoblastoma patients.\(^2^0-^2^2\) This is especially true for patients with bilateral retinoblastoma since the majority harbor inherited germline mutations which predispose to cancer. We attempted to assess the

### Table 3. Characteristics and outcome for patients who underwent high-dose chemotherapy and peripheral blood stem cell transplant for tumor at the surgical margin of the optic nerve and/or extrascleral extension.

<table>
<thead>
<tr>
<th>Study/date published</th>
<th>Study design</th>
<th>Study period</th>
<th>Country of origin</th>
<th>Number of patients</th>
<th>Indication</th>
<th>Response to induction chemotherapy</th>
<th>High dose chemotherapy</th>
<th>Adequate high-dose CTX regimen used?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Namouni et al(^2) 1997</td>
<td>Retrospective</td>
<td>1989-1994 France</td>
<td>6(^{*})</td>
<td>- 5 patients; involved cut end of optic nerve - 1 patient; extrascleral extension</td>
<td>All patients achieved CR</td>
<td>CEC</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Kremens et al(^4) 2003</td>
<td>Retrospective</td>
<td>1992-2001 Germany</td>
<td>1(^{*})</td>
<td>Involved cut end of optic nerve and extrascleral extension</td>
<td>CR</td>
<td>CTE</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>

CEC: Cyclophosphamide, Etoposide, Carboplatin; CTE: Carboplatin, Thiotepa, Etoposide; EBRT: external-beam radiation therapy; NED: no evidence of disease; CR: Complete response; \(^{*}\)Both studies included patients with involved cut end of optic nerve/ extrascleral extension and patients presenting with disease relapse/distant metastases.

### Table 3 cont. Characteristics and outcome for patients who underwent high-dose chemotherapy and peripheral blood stem cell transplant for tumor at the surgical margin of the optic nerve and/or extrascleral extension.

<table>
<thead>
<tr>
<th>Study/date published</th>
<th>Type of HSCT</th>
<th>Other treatments in addition to transplant</th>
<th>Enucleation</th>
<th>Median follow-up period in months (range)</th>
<th>Toxicity (number of patients affected/total number of patients)</th>
<th>Treatment related mortality</th>
<th>Functional eye preservation</th>
<th>Survival</th>
<th>Second malignancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Namouni et al(^2) 1997</td>
<td>Auto in all patients</td>
<td>All patients received EBRT</td>
<td>No</td>
<td>29.5 (9-55)</td>
<td>Not clear(^{a})</td>
<td>None</td>
<td>Not clear</td>
<td>All but one patient were alive NED at time of F/U</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Kremens et al(^4) 2003</td>
<td>Auto</td>
<td>None</td>
<td>NA</td>
<td>8 (NA)</td>
<td>Grade III and IV GI toxicity</td>
<td>None</td>
<td>Involved eye enucleated before treatment</td>
<td>Alive NED</td>
<td>Not mentioned</td>
</tr>
</tbody>
</table>

CEC: Cyclophosphamide, Etoposide, Carboplatin; CTE: Carboplatin, Thiotepa, Etoposide; EBRT: external-beam radiation therapy; NED: no evidence of disease; CR: Complete response; \(^{a}\)Both studies included patients with involved cut end of optic nerve/ extrascleral extension and patients presenting with disease relapse/distant metastases.
incidence of second malignancy in our review; however, and due to the short follow-up in most cases, most of the studies did not mention the occurrence of second malignancies in their respective patients. Furthermore, a significant proportion of the reviewed patients received radiotherapy in addition to high-dose chemotherapy (38 patients), and as such, we were unable to derive rigid conclusions on the incidence of second malignancy in retinoblastoma patients treated by high-dose chemotherapy followed by stem cell transplantation. In addition, radiation therapy has been linked with compromising the development and growth of orbital and facial bones during childhood. As a consequence, parents are often reluctant to accept this potential side effect of external-beam radiation therapy. In these situations, high-dose chemotherapy followed by stem cell transplantation poses as an alternative approach to adjuvant radiation therapy.

In conclusion, this study represents the first detailed systematic review addressing the role of high-dose chemotherapy followed by stem cell transplantation in retinoblastoma patients. High-dose chemotherapy (using a platinum agent, an alkylating compound and etoposide) followed by stem cell transplantation is an effective and well-tolerated treatment strategy in patients with retinoblastoma. Durable tumor control is possible in patients with non-CNS metastases, with trilateral or bilateral advanced retinoblastoma, and in patients with tumor at the surgical margin of the optic nerve and/or extrascleral extension. Patients with CNS metastases require thiopeta to improve tumor control.

Conflict of Interest
The authors have no conflicting interests.

Author contributions
IJ, AS, AA: draft of manuscript and approval for publication; All authors: approval for publication

REFERENCES