Brief Communication

Systemic Chemotherapy in Retinoblastoma: Anaesthetic Implications

Julius Scott[1], *Suganeswari G*[2]

[1]Sri Ramachandra Institute of Higher Education and Research, Chennai

[2]Senior Consultant, Vitreoretina and oncology services, Sankara Nethralaya, Chennai

Retinoblastoma is one of the most common primary paediatricintraocular malignancy arising from embryonic neural retina. It accounts to 3% of cancers among children less than 15 years. Annual incidence of retinoblastoma across the globe is 15,000 to 20,000 live births. Retinoblastoma gene RB1 is a tumour suppressor gene located on the long arm (q) of chromosome 13 (13q14.). A retinoblastoma forms when both copies of the RB1 gene are affected by a gene alteration (mutation). Inheritance is either hereditary or sporadic. Sporadic is prevalent and accounts to 60% while heritable accounts to 40%. It neither has gender nor laterality predilection. The nternational Classification for Intraocular Retinoblastoma is based on the extent of the cancer and on the chances that the eye can be saved using current treatment options.

Address for correspondence:

Dr.Julius Scott

Head, Division of Pediatric Hematology and oncology, Sri Ramachandra Institute of higher education and research

Porur, Chennai 600116.

Article History

Received: 25th November 2020

Revision: 9th December 2020

Accepted: 12th January 2021

Published: 14th January 2021

This staging system is widely accepted and currently in use. Intraocular retinoblastomas are divided into 5 groups labelled from A to E.

Retinoblastoma is both chemo and radio-sensitive. The treatment of the retinoblastoma has evolved from primarily enucleation to highly selective methods of chemotherapy administration. Chemotherapy was introduced in the 1950s and has become an integral component in management of RB. At one time, chemotherapy was used mainly to manage metastatic retinoblastoma, but later used for non-metastatic retinoblastoma. Now, four main routes of administration of chemotherapy are present, and these are: intravenous chemotherapy (IVC), intra-arterial chemotherapy (IAC), intra-vitreal chemotherapy (IVitC) and periocular chemotherapy (POC).

The likely complications and systemic toxicities of IVC are important to be looked at carefully before any anaesthetic procedures.

How to cite this article: Julius Scott, Suganeswari G. Systemic Chemotherapy in Retinoblastoma: Anaesthetic Implications. Indian J Ophthal Anaesth 2021;1(1): 44-8

Intravenous chemotherapy for retinoblastoma (IVC)

In 1953 Carl Kupfer reported the successful use of intravenous nitrogen mustard along with irradiation to treat a child with recurrent retinoblastoma thereby starting the era of chemotherapeutic treatment for retinoblastoma.[1] In the early 1990s use of systemic chemotherapy was popularized and strongly advocated. The use of external beam radiation was restricted in favour of chemotherapy due to the considerable risk of secondary tumours in patients receiving radiotherapy. IVC is used in patients with intraocular disease only with or at high risk of extraocular disease. When the disease is limited to the eyes, IVC aims at shrinking the size of the tumour to expedite cure and lessen the damage induced by consolidating local therapies to follow, especially when the tumour involves sensitive retinal areas such as the macula. This has been termed chemo-reduction and it had been shown to achieve adequate tumour control and eliminated the need for enucleation or external beam radiation (EBR) in more than 75% of patients in a large series.[2]

IVC is used also as an adjuvant therapy after enucleation in patients with extraocular disease (metastasis) as well as patients with intraocular disease associated with high-risk histopathological features (e.g., optic nerve invasion beyond the lamina cribrosa and choroid invasion >3 mm) demonstrated on histopathological examination of the enucleated eye.[3]

It is speculated that patients with high-risk features might presumably have micro-metastasis and administering systemic chemoprophylaxis helps in improving their prognosis. Evidence in the literature supports the use of prophylactic IVC in high-risk patients and it is safe and effective in decreasing the risk of metastasis.[4]

Systemic chemotherapy as neo-adjuvant

Indications

I) To facilitate ocular salvage by achieving chemo reduction making the tumour more amiable to local therapy.

ii) To reduce the need for external beam radiation with a view to limiting the late effects.

iii) When upfront enucleation may not be immediately acceptable to the families.

Systemic chemotherapy as Adjuvant chemotherapy

Indications

High Risk Features on pathology where **6 cycles of Standard dose** adjuvant chemotherapy are indicated:

i) Anterior segment invasion

ii) Ciliary body infiltration

iii) Any choroidal invasion (invasion 3 mm in basal diameter or thickness)

iv) Retro-laminar optic nerve invasion

v) Combination of optic nerve infiltration till pre-laminar/laminar along with one more high risk feature.

High Risk Features on pathology where **high-dose** adjuvant chemotherapy **12 cycles** are indicated :

i) Full thickness scleral extension
ii) Extrascleralextension
iii) Optic nerve invasion at line of transaction

Indications for standard dose chemotherapy

1. Intraocular retinoblastoma Group A to E
2. Histo-pathological high risk factors following enucleation (massive choroidal invasion, anterior segment invasion and retro-laminar optic nerve invasion not involving transected margin)

Indications for high dose chemotherapy

1. Extraocular retinoblastoma (orbital extension or optic nerve involvement on imaging)
2. Histo-pathological high-risk factors (Full thickness scleral invasion, Extra scleral extension, optic nerve involvement till transection)

Metastatic disease

Patients with CNS involvement usually have a very poor prognosis with low survival rate. The usual approach consists of platinum-based IVC with agents having good CNS penetration along with focal CNS treatments such as radiotherapy. Distant metastasis usually occurs to the bone and promising results using cisplatin based regimens and consolidation with high dose chemotherapy and autologous hematopoietic progenitor cell rescue is reported in a small group of patients.[5]

Salvage therapy

In children who failed first line of treatment, systemic therapy with cyclophosphamide and topotecan was reported to be effective in globe preservation.[6]Topotecan combined with vincristine and carboplatin with aggressive focal therapies have been found to be effective regimen in advanced retinoblastoma and resulted in globe salvage with vision.[7]

Chemotherapeutic protocol

The most commonly employed IVC therapy is the VEC protocol: Vincristine, Etoposide, Carboplatin in standard doses based on the body weight. Higher doses may be used in patients with more advanced disease (bilateral group D or E).[8]The Standard and high dose VEC regimens followed is shown in Table 1 and Table 2 respectively. In high risk pathology cases, VEC is used alone or alternating with cyclophosphamide and doxorubicin.The goals of RB treatment are firstly patient survival, then protection of the eye and finally visual function

Table 1. Standard dose VEC regimen

Drugs	< 3 years		>3 years	
	Dose	Duration	Dose	Duration
Vincristine	0.05 mg/kg/day	1 day	1.5mg/m2/day	1 day
Carboplatin	18.6mg/kg/day r	1 day	560mg/m2/day	1 day
Etoposide	5 mg/kg/day	2 days	150 mg/m2/day	2 days

Table 2. High dose VEC regimen

Drugs	Dosage	Duration
Vincristine	0.025 mg/kg/day	1 day
Etoposide	12mg/kg/day	2 days
Carboplatin	28mg/kg/day	1 day

Side effects of chemotherapy

Vincristine – Headache, mental depression, dizziness, convulsions, anemia, leukopenia, thrombocytopenia and hepatic impairment (hepatic veno-occlusive disease –VOD, hepatitis)

Etoposide–nausea, vomiting, diarrhea, hypotension(if injected rapidly), thrombocytopenia, leukopenia.

Carboplatin – dizziness, confusion, tinnitus, ototoxic, hepato and renal toxic, cytopenia, electrolyte imbalance

Nadir (Point in time between chemotherapy cycles in which low blood counts will be detected) will be seen in the second week of chemotherapy and usually resolves in the third week. Doxorubicin cardio-toxicity can be acute, occurring during and within 2–3 days of its administration. The incidence of acute cardio-toxicity is approximately 11%.[9,10] The manifestations are usually chest pain due to myopericarditis and/or palpitations due to sinus tachycardia, paroxysmal non-sustained supraventricular tachycardia and premature atrial and ventricular beats. The mechanisms for these acute changes are not clear but may be due to doxorubicin-induced myocardial oedema, which is reversible.[9,11]

Acute left-ventricular (LV) failure is a rare manifestation of acute cardio-toxicity, but it is also reversible with appropriate treatments.

Pre anesthetic Implications

Complete blood count must be checked prior to any anesthetic procedures.

Liver function tests, renal function parameter (urea, serum creatinine) and serum electrolytes test to be performed prior to initiation of every cycle of chemotherapy.

Children receiving doxorubicin should have echocardiogram done after every 2 cycles.

It is also important to remember during pre-anaesthetic evaluation that orbital disease could have CNS involvement during the course of treatment. Hence, if there is a subtle sign of raised intra cranial tension, it should be evaluated with imaging.

Conclusion

Pre-anaesthectic evaluation for all retinoblastoma children post chemotherapy should include evaluation for cytopenia, liver and renal function, electrolyte level and if anthracyclines are received then cardiac evaluation must be done.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Kupfer C. Retinoblastoma treated with intravenous nitrogen mustard. American Journal of Ophthalmology. 1953;36(12):1721-23.
2. Shields CL, Mashayekhi A, Cater J, Shelil A, Meadows AT, Shields JA. Chemoreduction for retinoblastoma: Analysis of tumor control and risks for recurrence in 457 tumors. Transactions of the American Ophthalmological Society. 2004;102:35-44.
3. Eagle RC Jr. High-risk features and tumor differentiation in retinoblastoma: A retrospective histopathologic study. Archives of Pathology & Laboratory Medicine. 2009;133(8):1203-9.
4. Honavar SG, Singh AD, Shields CL. Post-enucleation adjuvant therapy in high-risk retinoblastoma. Archives of Ophthalmology. 2002;120(7):923-31.
5. Dunkel IJ, Khakoo Y, Kernan NA. Intensive multimodality therapy for patients with stage 4a metastatic retinoblastoma. Pediatric Blood & Cancer. 2010;55:55-9.
6. Qi C, Vasiliki A, Joan OB, Paul S.Topotoecan and Cyclophosphamide as salvage therapy in the treatment of Retinoblastoma. Investigative Ophthalmology & Visual Science 2013;54:3977.
7. Brennan RC, Qaddoumi I, Mao S, et al. Ocular Salvage and Vision Preservation Using a Topotecan-Based Regimen for Advanced Intraocular Retinoblastoma. J ClinOncol 2017;35(1):72-7.
8. Shields CL, Lally SE, Leahey AM, et al. Targeted retinoblastoma management: When to use intravenous, intra-arterial, periocular, and intravitreal chemotherapy. Current Opinion in Ophthalmology. 2014;25(5):374-85.
9. Takemura G, Fujiwara H. Doxorubicin-induced cardiomyopathy from the cardiotoxic mechanisms to management. ProgCardiovasc Dis. 2007;49:330–52.
10. Swain SM, Whaley FS, Ewer MS. Congestive heart failure in patients treated with doxorubicin. A retrospective analysis of three trials. Cancer. 2003;97:2869–79.
11. Singal PK, Deally CM, Weinberg LE. Subcellular effects of Adriamycin in the heart: a concise review. J Mol Cell Cardiol. 1987;19:817–28.