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Does Intra-Arterial Chemotherapy for Retinoblastoma cause more Systemic Metastases than Intravenous Chemotherapy?

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Abbreviations: CVA: Cerebrovascular accidents; EBRT: External Beam Radiation Therapy; IAC: Intra-arterial chemotherapy; IVC: Intravenous chemotherapy; RB: Retinoblastoma

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Retinoblastoma (RB), a common primary intraocular tumor in children is life threatening if not treated properly. Various treatment options to treat retinoblastoma include radiotherapy (external beam radiotherapy, plaque brachytherapy, and proton beam irradiation), chemotherapy (intravenous, periocular, intravitreal, intra-arterial), & laser photocoagulation and combination therapies [1-4]. With each treatment method though the retinoblastoma regresses either completely or partially, they have exhibited some side-effects. External beam radiotherapy (EBRT) and plaque brachytherapy were known to cause radiation induced complications and second malignancies. The well known side effects of systemic intravenous chemotherapy (IVC) are blood dyscrasias (secondary leukaemias), neutropenia, neurotoxicity, nephrotoxicity, ototoxicity and immunosuppression. Systemic metastases was reported following IVC, however, it may be less compared with other treatment modalities such as radiotherapy [2, 5]. Since a decade, the systemic intravenous chemotherapy has been replaced (or combined) by intra-arterial chemotherapy for the treatment of retinoblastoma in young children [6-13].

Treatment with intra-arterial chemotherapy has regressed the early stage retinoblastoma (A, B, C) completely than the later stage tumors (stage D or E). Following IAC, globe salvage rates were higher compared with other modes of treatment. Ocular event free survival was reported to be higher following IAC as a primary treatment for retinoblastoma than with IVC or EBRT prior to IAC. The short-term side-effects of intra-arterial chemotherapy are eyelid edema, bulbar conjunctival congestion, retinal vasculopathy, ophthalmic artery spasm, vitreous hemorrhage, subretinal hemorrhage, vitreous seeding and transient myelosupression [6,7]. The long-term side effects are tumor recurrence, chorioretinal atrophy, rhegmatogenous retinal detachment, stroke/CVA and metastases [7-9]. Metastatic disease includes regional lymph nodes, distant metastases and central nervous system involvement. Many retrospective studies have reported the rates of metastasis after treatment with IAC for retinoblastoma in children. A retrospective multicenter study by Abramson et al, detected 3 metastatic deaths out of 1139 patients of retinoblastoma treated with intra-arterial chemotherapy over a period of 10 years. This multicenter study concluded that after treatment with IAC either as primary or secondary therapy in retinoblastoma children, the observed

deaths due to metastasis were less than 1% [10]. Meta-analysis of 26 studies comprising of 1541 eyes comparing IAC (n = 445 eyes) with IVC (n = 1096 eyes) revealed that the rate of metastases was little high with IAC (2.7%) than IVC (0.6%) in retinoblastoma patients. This study concluded that IAC is definitely superior to IVC especially for group D (group IV & V) in terms of globe salvage (79.5%) and overall high success rates (75.7%) [8]. In another meta-analysis by Yousef et al, there were reported 20 cases of metastasis in patients who had prior IAC [9]. Orbital metastasis was reported after super selective IAC for group E retinoblastoma in a child though local tumor regressed well [11]. However, some studies published no known metastasis following IAC for retinoblastoma patients. Approximately 4 years following IAC and intravitreal chemotherapy for either early or advanced stage of retinoblastoma, there was no evidence of metastasis, leukaemia's or extra-ocular extension in 66 patients [12]. Another study reported good vision recovery following IAC for retinoblastoma with no evidence of metastasis 9 years after IVC or 3.5 years after IAC [13].

Treatment options for metastatic disease are surgical excision, high dose salvage chemotherapy, autologous hematopoietic stem cell rescue therapy and radiotherapy depending on the site of metastasis.

In conclusion, when intra-arterial chemotherapy is given alone for the treatment of retinoblastoma, there were few reports of systemic metastasis than when combined with systemic intravenous chemotherapy or local intravitreal chemotherapy and periocular chemotherapy.

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