Chemotherapy in eye cancer

Chemotherapy is one of several treatment strategies used to halt the uncontrolled division, proliferation and unpredictable growth patterns of malignant cells.

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Cancer chemotherapy research is a multibillion-dollar industry, which began in the early 20th century when mustard gas was used in World War I as a chemical warfare agent and was found to be a suppressor of haematopoiesis.

Chemotherapeutic drugs work by impairing mitosis at the DNA and/or RNA level. The drugs are cytotoxic and kill cells by promoting apoptosis or frank necrosis. Chemotherapy may be intended to be either curative or palliative and is therefore used in several different ways. Chemotherapeutic drugs can be used in combination with radiation therapy and surgery, for chemoreduction preoperatively, and postoperatively when there is residual tumour or risk of recurrence, and as palliative therapy to decrease the tumour load and increase life expectancy.

Classification of chemotherapeutic agents

DNA damaging

Alkylating agents

These agents act by covalently binding alkyl groups. Their major effect is to cross-link DNA strands, interfering with DNA synthesis and causing strand breaks, e.g. cyclophosphamide, ifosfamide, melphalan and chlorambucil.

Platinum compounds

These agents cause interstrand cross-links of DNA and are regarded as non-classic alkylating agents, e.g. cisplatin and carboplatin.

Antimetabolites

These are structural analogues of naturally occurring metabolites that interfere with normal synthesis of nucleic acids by falsely substituting purines and pyrimidines in metabolic pathways. These compounds can be divided into:

- Folic acid analogues, e.g. methotrexate. It is structurally very similar to folic acid and binds preferentially to dihydrofolate reductase, the enzyme responsible for conversion of folic acid to folinic acid. It is used for solid tumours, haematological malignancies and as an immunosuppressant in non-malignant inflammatory conditions, e.g. rheumatoid arthritis.
- Pyrimidine antagonists, e.g. 5-fluoro-uracil (5-FU), cytosine and arabinoside (cytarabine). 5-FU consists of a uracil molecule with a substituted fluorine atom. It acts by blocking the enzyme thymidylate synthetase essential for pyrimidine synthesis.
- Purine antagonists, e.g. 6-mercapto-purine and 6-thioguanine, used exclusively in the treatment of acute leukaemia.

DNA repair inhibitors

Epipodophyllotoxins

These are semi-synthetic derivatives of podophyllotoxin, which is an extract from the mandrake plant. For example, etoposide is a drug used in a wide range of cancers, which produces DNA strand breaks by acting on the enzyme topoisomerase II.

Cytotoxic antibiotics

These act by intercalating adjoining nucleotide pairs on the same strand of DNA and by inhibiting DNA repair, e.g. doxorubicin (Adriamycin), bleomycin, mitomycin C and dactinomycin (actinomycin D).

Antitubulin agents

Vinca alkaloids

These act by binding to tubulin and inhibiting microtubule formation, e.g. vincristine (Oncovin) and vinblastine.

Taxanes

These bind to tubulin and prevent assembly into microtubules, e.g. paclitaxel and docetaxel.

Other

Biological response modifier

An example of this class of chemotherapeutic agents is the interferons. They are a family of naturally occurring glycoproteins that bind to cell surface receptors and trigger a cascade of intracellular activity, thus promoting antitumour and antiviral properties through direct and indirect mechanisms.

Immunosuppressive agents

Most immunosuppressive agents mainly affect T-cell functioning at an intracellular level, e.g. cyclosporin.

Chemotherapy in ophthalmology

Eyelid malignancies

Malignant lesions that affect the eyelids are basal cell carcinoma (BCC), squamous cell carcinoma (SCC), malignant melanoma and less often, sebaceous gland carcinoma (SGC) and Merkel cell carcinoma. The methods of treatment include surgical excision, cryotherapy, radiation, photodynamic therapy and chemotherapy.

The gold standard is surgical excision with clear tumour margins using the Mohs' micrographic surgery technique or excisional biopsy with frozen sections. These methods are not always curative with large, deeply invasive eyelid lesions and pose management problems. Chemotherapy has been reported to result in a decrease in tumour size and allows for less extensive surgical resections and/or radiation therapy.

5-FU, cisplatinum, doxorubicin, bleomycin and interferon have been used in some cases of extensive, deeply invasive lesions as intralesional or systemic chemotherapy, but reports in the literature are scanty and outdated.

One study by Morley *et al.*[1] reported the use of cisplatin-based combination systemic therapy for chemoreduction for BCC of

the eyelids. Their study consisted of a small sample size, but all patients showed a reduction in size and 50% complete regression. While not curative, cisplatinum was useful as an adjunct to decrease tumour mass prior to local excision and for patients who refuse or must delay exenteration.

Conjunctival malignancies

Several benign and malignant lesions affect the conjunctiva. These include primary acquired melanosis (PAM), melanoma, conjunctival/corneal intra-epithelia neoplasia (CCIN) and SCC. The therapeutic options include: local excision with cryotherapy, radiotherapy and exenteration in some advanced cases.

Malignant melanoma may arise *de novo*, from a pre-existing naevus or from PAM with atypia. It may invade just the cornea or extend into the orbit and adnexa. Lesions arising *de novo* are more localised, but those from PAM tend to be more diffuse and challenging to treat, and topical chemotherapy provides an alternative to extensive and repeated surgery.

Mitomycin C (MMC)

MMC is well known for its use in trabeculectomies to prevent bleb failure and in pterygium surgery to prevent recurrence. MMC has been shown in several studies to be effective in the treatment of conjunctival lesions. In a 10-year retrospective review of ocular surface neoplasia, MMC was shown to have a highly effective role as primary therapy for PAM and CCIN and to be useful as an adjunctive to surgery with cryotherapy, brachytherapy for SCC, melanoma and SGC with pagetoid spread.[2]

Interventional studies using MMC have used a combination of 0.02% or 0.04%. The use of 0.04% MMC qid for 14 days, then off for 3 - 4 cycles, is the most popular regimen in the literature, but the exact dosing regimen of MMC is highly variable, with some centres using it for 1-, 2-, 3- and even 4-week cycles.

Topical MMC chemotherapy used as primary treatment has a higher recurrence rate than if it is used as an adjunct to therapy. The recurrence rate for CCIN and SCC when used as primary therapy is 0 - 22%[2] and for PAM with atypia 13 - 38%.[2] The results for melanoma are highly variable with one study reporting a recurrence rate of 33 - 100%[2] and another reporting 0 - 100%.[3]

The side-effects of MMC range from transient, self-limiting, short-term sequelae to chronic, long-term complications. In a 10-year review[2] most of the short-term complications occurred during the second cycle of MMC therapy and only 7% of patients had to stop using MMC because of these side-effects. Long-term complications of MMC occurred in 33% of patients. The most common complication was persistent keratoconjunctivitis that could be managed effectively with topical therapy. The other complications were epiphora due to punctal stenosis and corneal changes and persistent corneal erosions due to limbal stem cell deficiency (LSCD) in 12% of patients.

5-fluorouracil (5-FU)

5-FU has also been shown to be effective in the treatment of CCIN.

Yeatts *et al*.[4] described a dosing regimen of 1% 5-FU 4 times a day for 4 days, repeated every month for 4 - 6 cycles, to decrease toxicity and maintain efficacy. This regimen seems to be better tolerated with fewer side-effects than 1% 5-FU 4 times a day for 2 weeks, as suggested in other studies.[5]

Studies have shown MMC and 5-FU to be effective as an adjunctive therapy following surgical excision with cryotherapy and effective as primary therapy in certain cases. The side-effect profile of these two drugs has been a problem in selected cases and has led to further research looking at drugs like interferon alpha (IFNα) to treat patients with ocular surface squamous neoplasia (OSSN).

Interferons (IFN)

A recent 10-year review by Karp *et al*.[6] demonstrated peri-lesional and/or subconjunctival IFNα2b as effective for the primary treatment of OSSN. Another study looking at giant (≥15 mm basal diameter or ≥6 limbal clock-hours) ocular surface neoplasia managed with topical and/or peri-lesional injections, as primary and/or adjunctive therapy, achieved complete control in 72% and reduction in size in 28%. Patients only reported transient flu-like symptoms associated with injection of IFNα2b and self-limiting ocular surface problems that could be related to the vehicle in the IFNα2b eyedrops.[7]

IFN are expensive but remain an attractive alternative owing to the relative lack of corneal or conjunctival toxicities, preservation of limbal stem cells and patient comfort compared with topical chemotherapy.

> **Malignant melanoma of the conjuctiva may arise** *de novo,* **from a pre-existing naevus or from PAM with atypia.**

Intraocular tumours
Retinoblastoma

Retinoblastoma represents approximately 4% of all paediatric malignancies and is the most common intraocular malignancy of childhood. It is estimated that 200 - 300 new cases of retinoblastoma are diagnosed in the USA each year and substantially more in developing countries. Over 95% of children in developed countries survive their malignancy, with only 50% surviving worldwide, because of late detection in developing countries.[8]

Retinoblastoma is a curable cancer, but there are three important life-threatening

aspects. These include: metastasis, intracranial neuroblastic malignancy (trilateral retinoblastoma) and secondary primary tumours. Management therefore requires a multi-disciplinary, experienced team with the goal of saving the patient's life, preserving the globe and lastly preserving vision.

Classification

Several classifications have been used to assist in prediction of globe salvage. The Reese-Ellsworth classification was conceived in the 1960s in the era of external beam radiotherapy and the International Classification of Retinoblastoma (ICRB) was introduced in 2003 to simply and appropriately stage the disease during the era of chemoreduction for retinoblastoma [8] (Table 1).

With the focus of treatment now including the preservation of vision, several new studies by the Children's Oncology Group (COG) and other institutions have looked at the use of chemoreduction for intraocular disease and focal chemotherapy for selected high-risk retinoblastoma.[9]

Systemic chemotherapy

Systemic chemotherapy using a combinationof vincristine, etoposide and carboplatin (VEC), with or without focal consolidation therapy, has been highly successful in retaining many eyes with visual function. Systemic chemotherapy also avoids radiation-induced side-effects, but exposes the entire body to significant doses of highly toxic drugs to treat a minute fraction (<1% by weight) of the body in some cases. Side-effects associated with systemic therapy include severe neutropenia, thrombocytopenia, fever, port infections, hearing loss and increased risk of developing acute myelogenous leukaemia. The literature has also reported that systemic chemotherapy is not effective in treating tumours associated with subretinal and vitreous seeds. This knowledge has encouraged exploration of focal drug delivery methods to reduce recurrence rates and long-term toxicity.[9]

Intra-arterial chemotherapy

As mentioned previously, chemotherapy has been highly effective in treating patients, but it seems to be less effective in treating group C and D eyes, which are associated with subretinal and vitreous seeds. These patients have been shown to have up to 45% recurrence of disease following systemic chemotherapy, and other authors have emphasised that, in the presence of vitreous seeds and subretinal seeds, enucleation should be carried out. The challenges of vitreal and subretinal seeds have been met with the use of intra-arterial chemotherapy.

The injection of chemotherapeutic agents into the carotid artery was first attempted by Reese in 1957. Japanese investigators have also catheterised the carotid artery to inject melphalan, but they combined hyperthermia and external beam radiotherapy (EBRT) to treat the patients in their study.

A phase I/II clinical trial[10] assessed the outcomes after ophthalmic artery cannulation for the delivery of intra-arterial melphalan to treat patients with advanced retinoblastoma (Reese-Ellsworth V). In this trial the ophthalmic artery was successfully cannulated with dramatic tumour, vitreous and subretinal seed regression. They also reported few transient side-effects in the 9 patients treated.

Another study by Abramson et al.[11] has shown a 2-year probability of ocular salvage of 80% for both vitreal and subretinal seeds in treatment-naïve eyes and 54% for eyes which had been previously treated.

Despite intra-arterial chemotherapy requiring a trained interventional radiologist and side-effects associated with embolic events to the globe, this form of treatment represents an exciting alternative to systemic chemotherapy.

Intravitreal chemotherapy

The use of intravitreal drugs to treat a host of ocular conditions has become standard practice over the last decade, and we have learnt that complications associated with intravitreal injections are extremely rare.

The main concern with the use of intravitreal injections for retinoblastoma is extra-ocular spread due to tumour seeding into the needle track.

A study by Smith et al.[12] used a combination of subconjunctival and intravitreal carboplatin to treat 2 patients with bilateral retinoblastoma and failed systemic chemotherapy. The subconjunctival injection was done prior

Table 1. Treatment strategy based on laterality and retinoblastoma grouping[8,9]

ICRB	Prognosis	Unilateral	Bilateral
A	Usually eradicated by treatment. Good visual and overall prognosis	Focal therapy (argon laser, cryotherapy, hyperthermia, brachytherapy)	Same
B	Too large to be treated with focal therapy alone. Visual prognosis excellent with treatment	VC + focal therapy or plaque	VC + focal therapy
C	Visual prognosis variable depending on location of tumour	VEC + focal therapy or plaque	VEC + STC*
D	Visual prognosis guarded depending on tumour location. Morbidity from focal therapy high	Enucleation or VEC + STC*	VEC + STC*
E	No visual potential. Morbidity with treatment is high	Enucleation	Enucleation but if both eyes equally advanced then VEC + STC* + low-dose EBRT

V – vincristine; C – carboplatin; E – etoposide; EBRT – external beam radiotherapy; ICRB – International Classification of Retinoblastoma; STC – sub-tenon carboplatin.

*Note: Periocular chemotherapy treatment using a sub-tenon injection of carboplatin has been associated with toxicity which is likely due to the rapid dispersal of the drug, but the use of a fibrin sealant allows for a controlled release for periocular delivery.

to intravitreal therapy to reduce the risk of orbital tumour seeding from the injection. Histopathological examination of the two enucleated eyes at 6 weeks post-injection revealed no patent pars plana injection site or malignant tumour seeding. This study highlights that the risk of tumour seeding is probably lower than previously expected.

Munier et al.[13] looked at the short-term efficacy of intravitreal melphalan for vitreal disease and found that globe retention was achieved in 87% and all retained eyes had complete remission after a mean follow-up of 22 months. The main ocular complication was a localised salt and pepper retinopathy noticed at the injection site.

> ## Chemotherapy may be intended to be either curative or palliative and is therefore used in several different ways.

Intravitreal chemotherapy is therefore being considered for patients with group C or D disease with recurrent and persistent vitreal or subretinal seeds. The technique involves intravitreal injection of 20 - 30 μg of melphalan via a 32G needle. After injection, 3 cycles of freeze and thaw cryotherapy are applied at the injection site. The eye is carefully shaken in all directions to enable even distribution of the drug. The injection is repeated every 7 - 10 days for up to 8 injections, if a response can be documented and until complete seed fragmentation is observed or complete response is achieved. The side-effects are retinal toxicity at site of injection, salt and pepper retinopathy, and transient vitreous haemorrhage.

In summary, the main advantage of intravitreal chemotherapy would be not to replace the standard treatment care for group C and D eyes, but to reduce the exposure to systemic chemotherapy as well as the indications for enucleation and/or EBRT.

Melanoma
Malignant melanoma of the uvea is usually treated with episcleral plaque brachytherapy, charged particle radiation therapy or enucleation. Other interventions include hyperthermia and transpupillary thermotherapy to reduce radiation-related complications.

Chemotherapy has no role in the management of primary uveal melanoma.

Metastatic choroidal melanoma usually occurs in 35 - 50% of patients within 5 years of diagnosis of choroidal melanoma. The sites of metastases are the liver, lung and brain. Intra-arterial chemotherapy, for focal liver metastases, is used to control metastatic spread but no standard chemotherapy protocol exists and treatment outcomes have been consistently disappointing.[14]

Lymphoma
Large cell lymphoma is the most common type of non-Hodgkin's lymphoma to involve the eye and is usually accompanied by CNS involvement. Treatment is challenging but consists of a combination of radiation and multi-agent primary chemotherapy.

Intravitreal chemotherapy has been shown to be effective to treat primary intraocular lymphoma. De Smet et al.[15] showed the efficacy of intravitreal methotrexate and thiotepa in the treatment of recurrent intraocular lymphoma.

Disseminated disease is treated with systemic chemotherapy that consists of the CHOP regimen:[16]

- Cyclophosphamide, an alkylating agent which damages DNA by binding to it and causing cross-links
- Hydroxydaunorubicin (also called doxorubicin or Adriamycin), an intercalating agent which damages DNA by inserting itself between DNA bases
- Oncovin (vincristine), which prevents cells from duplicating by binding to the protein tubulin
- Prednisone or prednisolone, which are corticosteroids.

This regimen can also be combined with the monoclonal antibody rituximab if the lymphoma is of B-cell origin; this combination is called R-CHOP or CHOP-R. In patients with a history of cardiovascular disease, doxorubicin (which is cardiotoxic) is often deemed to be too great a risk and is omitted from the regimen. The combination is then referred to as COP (cyclophosphamide, Oncovin, and prednisone or prednisolone)

or CVP (cyclophosphamide, vincristine, and prednisone or prednisolone).

Orbital tumours
Rhabdomyosarcoma
Rhabdomyosarcoma is the most common primary malignant neoplasm of the orbit in children. It consists of malignant cells that demonstrate evidence of skeletal muscle differentiation. It can be challenging to treat as it arises in a large variety of primary sites. The orbit is the primary site in 25% of cases, with other areas of the head and neck, genito-urinary, trunk and extremities making up the remaining locations.

Rhabdomyosarcoma is classified into histological subtypes that are of prognostic and therapeutic importance. The most common and favourable type is embryonal and the least favourable is alveolar. The other two histological types are pleomorphic and botryoid, which account for <10%, and are also associated with a favourable outcome.

The tumour staging system is based on the tumour site(s) involved, regional lymph node involvement and distant metastases. Primary involvement of the orbit with rhabdomyosarcoma is considered a favourable site and any primary tumour of the orbit without distant metastases is considered stage 1 according to the Intergroup Rhabdomyosarcoma Study Group (IRSG) modified TNM staging system. After surgery the tumour will be grouped according to the IRSG clinical grouping system (Table 2) and radiation and chemotherapy are carried out accordingly.

> ## Retinoblastoma is a curable cancer, but three important life-threatening aspects must be remembered.

In the current Soft Tissue Sarcoma Committee of the Children's Oncology Group (STS COG) trials the only patients who did not receive radiotherapy were those with completely resected embryonal tumours. For all other patients radiotherapy began between weeks 3 and 15 of chemotherapy, depending on the response to initial chemotherapy. Doses of 36 - 41.4Gy are generally used for microscopic disease

(group II), depending on the presence of regional lymph node involvement, and 45 - 50.4Gy for gross disease (group III), depending on the primary site (Table 3).

Standard treatment according to the IRSG/STS COG trials in North America consists of a combination of vincristine, dactinomycin and cyclophosphamide (VAC). Trials have shown comparable but not superior outcomes, with other combinations of active agents (Table 3). Based on the toxicity profile and the fact that VAC can be administered in a single day, VAC has therefore remained the 'standard' of treatment in North America for the past several decades.

Side-effects of this chemotherapy regimen include myelosuppression, febrile neutro- penia, peripheral neuropathy and hepatopathy. Efforts are made to reduce these chemotherapy-induced complications by ensuring age-dependent doses of dactinomycin and cyclophosphamide, especially in patients <36 months of age.

By applying the management principles discussed above the 5-year survival rate for embryonal cell type primary rhabdomyosarcoma is 85%.

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Table 2. Intergroup Rhabdomyosarcoma Study Group (IRSG) clinical grouping system[17]

Group	Description
I	Localised disease, complete excision, regional lymph node not involved
II	Total gross resection with evidence of regional spread
a	Grossly resected tumour with microscopic residual disease
b	Regional disease with lymph node, complete resection with no microscopic residual disease
c	Regional disease with lymph node, grossly resected, microscopic residual disease and/or histological involvement of the most distal regional lymph node in the dissection
III	Incomplete resection with gross residual disease
IV	Distant metastatic disease present at onset

Table 3. Intergroup Rhabdomyosarcoma Study Group IV recommendations[17]

Group	Radiation therapy	Chemotherapy
I	None	VA x 32 weeks
II	36 - 41.4 Gy	VA x 32 weeks
III	45 - 50.4 Gy CFI *or*	VA + C x 52 weeks
	5.9 Gy HFI	*or*
		VA + I x 52 weeks
		or
		VI + E x 52 weeks

CFI – conventional fractionated irradiation; HFI – hyperfractionated irradiation; V – vincristine; A – actinomycin D; C – cyclophosphamide; I – ifosfamide; E – etoposide.

IN A NUTSHELL

- In the last decade there have been several advances in the knowledge and understanding of chemotherapeutic drugs for the treatment of ocular cancer.
- These drugs show improved long-term survival for patients but are unfortunately associated with toxic effects and multiple local and systemic complications.
- The use of focal chemotherapy is growing in popularity and represents an exciting new option to reduce systemic toxicity and ocular morbidity. Studies on the long-term effects of topical, subconjunctival, subtenon and intravitreal therapies are still required to determine their exact role as therapeutic agents.