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Review

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Cancer drugs and diabetic retinopathy: a dangerous, underestimated association

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Abstract

The worldwide growing prevalence of diabetes and cancer led to an increase in subjects affected by both these diseases that share several of the involved risk factors and have a complex, multifactorial etiopathogenesis. Cancer therapies could have harmful effects on several organs, particularly in subjects also affected by diabetes and its related comorbidities. Moreover, cancer diagnosis often monopolizes the attention of both patients and caregivers, thus reducing the attention to pre-existent diseases. Retinopathy is one of the most frequent microvascular complications of diabetes, accounting for about 5% of legal blindness worldwide. The retinal neurovascular unit is dysfunctional in diabetes and could represent a frail site when cancer therapies are administered. Nevertheless, the short- and long-term effects of the different anticancer molecules on retinal tissue, especially in diabetic subjects, are poorly known, and no specific recommendations on their prevention and management are available. In this review, we summarised the current data on this topic, focusing on the different cancer class drugs involved in retinal damage: anti-oestrogen, classical cytolytic chemotherapy (alkylating agents, taxanes, topoisomerase inhibitors, and antimetabolites), mitogen-activated protein kinase, tyrosine-kinase, and vascular endothelial growth factor inhibitors are the cancer drugs associated with retinal damage and visual disturbance. However, further studies are necessary to improve knowledge on the molecular and clinical relation between cancer therapies and retinopathy, in order to provide clinicians with evidence-based protocols to optimise the management of these conditions and minimise vision loss occurrence, impaired quality of life, and public health expense.

Keywords: Diabetes, cancer, retinopathy, blindness, chemotherapy, obesity, chronic complications, hypertension

INTRODUCTION

Diabetes mellitus (DM) and cancer are widespread diseases with a worrisome impact on public health systems. Currently, DM affects more than one in ten adults: the prevalence of DM is estimated to be about 540 million cases worldwide, rising to 780 million in the next two decades[1]. Likewise, the International Agency for Research on Cancer reported 19.3 million new cases of cancer and 10 million cancer-related deaths in 2020 and the global cancer burden is expected to be 28.4 million cases within 2040[2]. The growing prevalence of these diseases led to an increase in subjects affected by both T2D and cancer, and epidemiologic observations indicated that up to 20% of patients with cancer are also affected by DM, mainly type 2 (T2D)[3]. In particular, subjects with diabetes have an increased risk for liver, breast, pancreas, colorectal, bladder, and endometrium cancer[4,5]. These diseases share some of the involved risk factors and have a complex, multifactorial, not fully understood etiopathogenesis[6,7]. Insulin resistance and hyperinsulinemia induce cell growth favouring cancer progression and aggressiveness, mediated by the overexpression in tumoral tissue of the isoform A of the insulin receptor that has mostly mitogenic effects[6,8].

Anticancer drugs could have several harmful effects on cancer patients with diabetes. Indeed, the most common chemotherapies, together with reduced attention to diabetes management following cancer diagnosis, could directly and indirectly (increasing glycaemia) affect glucose metabolism and the course of diabetes-related micro- and macro-vascular complications[9,10].

Diabetic retinopathy (DR), occurring in about 30%-40% of diabetic individuals, is one of the most frequent microvascular complications of DM, and the most frequent cause of new cases of blindness in adults aged 20-74 years in developed countries[11]. The main determinants of DR are diabetes duration, glucose control, hypertension, and dyslipidaemia[12-14]. Moreover, unhealthy lifestyles (unbalanced diet, low level of physical activity, tobacco consumption), genetic and epigenetic mechanisms could contribute to the onset and progression of DR[15-17].

Retinal damage induced by cancer drugs includes a wide spectrum of disorders, reflecting the anatomical, physiological, and biochemical features of this tissue. The retinal neurovascular unit, composed of blood vessel, pericytes, neurons, and glia, is dysfunctional in DR and could represent a frail, target site for cancer drugs complications[18]. The knowledge of the retinal adverse effects is mandatory to address a personalised cancer treatment, in particular in subjects with diabetes, often affected by other comorbidities and vascular complications. Additionally, the prediction of cancer treatment ocular side effects may provide the opportunity to develop intervention strategies to recognize the tissue damage early before the occurrence of the visual impairment. Few data exist regarding the impact of anticancer chemotherapies on diabetes vascular complications, as well as no specific recommendations on their management in cancer patients are available.

In this review, we summarise the current evidence regarding the effect of the different anticancer therapies on the DR course. A literature search was conducted on PubMed, Embase, Web of Science, including studies from inception to date. We found case reports/series, observational, prospective, registry, and pre-registering trials, while no randomised controlled trials focused on the retinal effects of anticancer drugs in diabetes subjects were available. We aimed to provide clinicians with some advice for the best management of these patients, and to prevent the risk of retinal injury, vision loss, impaired quality of life, and public health expenses.

RETINAL EFFECTS OF THE DIFFERENT ANTICANCER DRUG CLASSES

Anti-oestrogen

Antioestrogen is used in the management of breast cancer. Ocular side effects of hormone therapy are less frequent than other organ toxicity, although their incidence is probably underestimated[19].

In particular, tamoxifen is an oral selective oestrogen receptor modulator used in the treatment of hormone receptor-positive breast cancer. Tamoxifen binds competitively to the cytoplasmic oestrogen receptors, entering the nucleus and inhibiting DNA synthesis, and its use is related to retinal thromboembolism[19]. Tamoxifen penetrates the choriocapillary barrier and induces glycosaminoglycan deposition in the plexiform layers of the retina nerve fiber, determining axonal injury[18].

A retrospective analysis of "The International Breast Cancer Study" evaluated, in a large number of subjects, the ocular toxicity related to adjuvant hormonal treatment (tamoxifen or toramifen) for breast cancer[20] [Table 1]. The authors reported the occurrence of retinal adverse events during hormone therapy in about 1% of the cohort, although other cohorts observed a 6% incidence[21]. The main retinal alterations include refractile yellowish deposits in the area surrounding macula, nerve, and plexiform layers. In the case of extensive deposits, macular oedema and visual acuity reduction occurred. These features regressed after tamoxifen withdrawal, although retinal deposits were permanent. The cumulative dosage of tamoxifen and duration of treatment could predict the risk for retinal damage, with the deposits occurring as the cumulative dosage approaches 100 g[19].

Few data are available on the risk for onset or progression of retinopathy in diabetic subjects treated with tamoxifen [Table 1]. Moussa and colleagues observed the onset of superficial retinal haemorrhages, exudates and macular oedema, in a 52-year-old woman who presented with blurry vision, a history of well-controlled T2D, and breast cancer previously treated with tamoxifen[22].

Similar retinal alterations were reported by Bommireddy and colleagues in a 52-year-old, non-diabetic woman who, at the time of visual impairment, was taking for about 5 years, 20 mg/day of tamoxifen to treat a grade 2, invasive lobular breast cancer[23]. Although the incidence of ocular toxicity during hormonal therapy is low, subjects treated with tamoxifen should be alerted of this possible side effect to promptly ruling out an ophthalmic evaluation in case of visual injury[20].

Androgen deprivation therapy

Anti-androgen drugs represent the standard of care for the treatment of prostate cancer both in adjuvant therapy and for the treatment of recurrence or biochemical failure[24].

Gonadotropin-releasing hormone agonists, as well as steroidal (cyproterone acetate) and nonsteroidal anti-androgens (flutamide, bicalutamide, and nilutamide), have a detrimental effect on body weight, fat composition, and insulin sensitivity, determining in diabetic subjects a worsening of glucose control[4,25,26]. The risk for DR is tightly related to the level of glucose control and insulin resistance; nevertheless, very limited evidence is available on the influence of anti-androgen on retinal health. In a large retrospective cohort observing 5,336 men newly diagnosed with localised prostate cancer and affected by pre-existing T2D, no significant increased risk for DR was reported in the group treated with androgen deprivation therapy. These men were treated with gonadotropin hormone-releasing hormone (GnRH) analogues (leuprolide, goserelin, or triporelin) or GnRH antagonists (abarelix or degarelix), with or without an oral anti-androgen (flutamide, bicalutamide, or nilutamide)[24]. Recently, we retrospectively evaluated the retinal short-term effects of cancer drugs in 168 patients with different cancer types (mean age 55.7 years) and

Table 1. Retinal effects of anticancer drug classes

Class/molecule	Study type and country	Cancer type	Rate of RAEs	Diabetes	Retinal features	Clinical evolution	Refs
Anti-oestrogen							
Tamoxifen or toramifen	Retrospective analysis of a multicentre international trial	Breast	0.9%	Yes (not indicated the prevalence in the whole cohort)	Refractile yellowish deposits (macula, nerve, and plexiform layers) Macular oedema	Regression after tamoxifen withdrawal, although retinal deposits were permanent	[20]
Tamoxifen	Case report of a 52-yo woman (USA)	Breast	-	Yes	Retinal haemorrhages Exudates Macular oedema	Regression of macular oedema after intraocular injection of Bevacizumab	[22]
Tamoxifen	Case report of a 52-yo woman (UK)	Breast	-	No	Refractile deposits (fovea, macula) Macular intraretinal cysts	Six months after tamoxifen withdrawal, no significant change in the retina was observed	[23]
Alkyl agents							
Carboplatin Cisplatin Oxaliplatin	Retrospective (Italy)	Lung Breast Colorectal	-	Yes	NPDR Cystoid macular oedema (cisplatin)	-	[15]
Cisplatin	Case report of a 31-yo man (UK)	Testis	-	No	Cotton wool spots Retinal haemorrhages Retinal neovascularization	Retinal signs did not improve after cisplatin discontinuation and laser photocoagulation	[33]
Topo Inhib							
Etoposide Doxorubicin	Retrospective (Italy)	Lung Liver	-	Yes	NPDR or PDR	-	[15]
Taxanes							
Paclitaxel	Case report of a 49-yo woman (Italy)	Ovarian		No	Cystoid macular oedema	Retinal signs disappeared after drug cessation	[30]
Paclitaxel or docetaxel	Prospective (Lebanon)	Breast Ovarian Esophagus	-	No	Increased central macular thickness, without significant macular oedema	-	[31]
Antimetabolites							
Gemcitabine	Case report of a 58-yo man (France)	Bladder	-	Yes	Microaneurysms Cotton wool spots Haemorrhages Increased macular thickness Mild retinal oedema	Retinal signs disappeared after drug cessation	[34]
5-FU	Case report of a 60-yo man	Stomach	-	Yes	Cystoid macular oedema	Retinal signs disappeared after drug cessation	[35]

	(Japan)						
Alkyl agents + Taxanes							
Carboplatin + paclitaxel	Case report of a 59-yo man (Japan)	NSCLC	-	Yes	Retinal ischaemia Soft exudates Haemorrhages	After changing anticancer drugs, the soft exudates and haemorrhages disappeared	[28]
Carboplatin + paclitaxel	Case report of a 70-yo woman (Egypt)	Cervix uteri		No	Retinal ischaemia Cotton wool spots	Retinal signs disappeared after drugs cessation	[29]
Alkyl agents + Topo inhib							
Cisplatin + etoposide	Case report of a 4-yo and 7-yo girls (USA)	Retroperitoneal malignant mixed germ cell tumour and liver cancer	-	No	Retinal granular pigmentation Optic nerve pallor	Retinal and optic nerve signs were permanent	[32]
MAPK inhib							
Pimasertib	Prospective (Netherlands)	Cutaneous melanoma	100%	Yes (not indicated the prevalence in the whole cohort)	Sub-retinal fluid	Retinal signs disappeared despite the continuation of the drug	[39]
Pimasertib	Case report of a 26-yo woman (Canada)	Ovarian	-	No	Outer retinal layer separation	Retinal signs disappeared after drug cessation	[37]
Selumetinib	Case report of a 13-yo girl and 6-yo boy (USA)	Pilocytic astrocytoma	-	No	Outer retinal layer separation	Retinal signs disappeared after drug cessation	[38]
Binimetinib	Prospective (Netherlands)	Cutaneous/uveal melanoma	60%-77%	No	Subretinal fluid	Retinal signs disappeared despite the continuation of the drug	[40]
Binimetinib	Phase 1 study	Various solid cancers	62%	Not indicated	Retinal detachment	Retinal signs improved, in most of the cases, after stopping the drug	[41]
MAPK+BRAF inhib							
Trametinib + dabrafenib	Case report of a 39-yo woman (Spain)	Cutaneous melanoma	-	No	Serious retinal detachments Extra-macula retinal fibrosis	Permanent extensive extra-macula retinal fibrosis	[42]
Tyrosine-kinase inhib							
Imatinib	Case report of a 62-yo man (USA)	GIST	-	No	Mild retinal haemorrhages Neovascularization	Retinal signs disappeared after drug dose reduction	[43]
Imatinib	Prospective (Italy)	Chronic myeloid leukemia	1%-2%	Yes (not indicated the prevalence in the whole cohort)	Retinal haemorrhages	Retinal signs usually disappeared after drug cessation	[44]
VEGF inhib							
Pazopanib							

Sorafenib Sunitinib	Registry multicentre international study	-	15%	No	Retinal haemorrhages Retinal detacòò 4ùhments Macular oedema	Retinal signs disappeared after drug cessation	[46]
FGFR inhib							
Infigratinib	Multicentre, open-label, single-arm, phase 2 study		17%	Not indicated	Chorioretinopathy Subretinal fluid Serious retinal detachment.	-	[47]
AZD4547	Open-label, single-arm phase 2 study		50%	Not indicated	Subretinal fluid	Subretinal fluid did not require any dose interruptions or reductions, and disappeared after the last dose.	[48]
ICIs							
Ipilimumab	Case report of a 70-yo woman (USA)	Cutaneous melanoma	-	No	Serious retinal detachments Subretinal fluid	After 6 weeks of ipilimumab withdrawal and glucocorticoid therapy, the retinal sign disappeared.	[51]
Nivolumab	Case report of a 64-yo woman (USA)	NSCLC	-	No	Narrowing of the retinal vessels Retinal thinning Vitreous detachment	Resolution after nivolumab discontinuation and glucocorticoid treatment	[52]
HER2 inhib							
Trastuzumab	Case report of a 50-yo woman (France)	Breast	-	No	Retinal hard exudates Retinal haemorrhages Macular oedema	Resolution after trastuzumab discontinuation	[54]

RAE: retinal adverse events; yo: years old; Alkyl: alkylating; NPDR: non-proliferant diabetic retinopathy; Topo: topoisomerase; Inhib: inhibitors; PDR: proliferant diabetic retinopathy; 5-FU: 5 fluorouracil; NSCLC: non-small cells lung cancer; MAPK: mitogen-activated protein kinase; GIST: gastro-intestinal stromal tumour; VEGF: vascular endothelial growth factor; FGFR2: fibroblast growth factor receptor 2; ICIs: immune check point inhibitors; HER2: human epidermal growth factor receptor 2.

previously diagnosed T2D (mean diabetes duration 9.3 years)[10,15]. In the subgroups of subjects (6% of the study cohort) treated for prostate cancer with anti-androgens, we did not observe an increased risk for short-term adverse retinal outcomes[10,15]. Further prospective, larger studies are necessary to better investigate these findings.

Classical cytolytic chemotherapy

Alkylating agents, anti-microtubule agents, antimetabolites, and topoisomerase inhibitors are currently used for the treatment of many cancers and could be associated with various degrees of hyperglycaemia in patients previously not affected by diabetes[27]. A toxic effect of these drugs on retinal tissue has been occasionally observed in subjects with and without diabetes mellitus [Table 1]. In a real-world retrospective study including cancer patients also affected by T2D for an average of 9 years, the use of alkylating agents and topoisomerase inhibitors was related to a seven- and nine-fold increase, respectively, of short-term retinal worsening[15]. This risk was more pronounced in obese subjects.

The combined treatment with alkylating agents and taxanes is common in various solid malignancies. Some reports described the different degrees of retinal toxicity due to the contemporary use of carboplatin and paclitaxel. Matsuyama and colleagues described the case of a 59-year-old man with good diabetes control (glycated haemoglobin 5.8%) and treated with both paclitaxel and carboplatin for a non-small cell lung cancer, who experienced severe visual loss due to a large number of bilateral soft exudates, retinal ischaemia, and haemorrhages. This retinal injury was resistant to laser photocoagulation and disappeared after stopping cancer treatment[28]. The case of paclitaxel and carboplatin retinal damage was described in a non-diabetic 70-year-old female affected by cervical cancer: bilateral mild decreased vision appeared four weeks after initiating chemotherapy, including 4 cycles of paclitaxel (175 mg/m^2) and carboplatin. Retinal examination showed an early ischemic retinopathy and cotton wool spots. Both symptoms and retinopathy signs disappeared after drugs cessation[29].

Several mechanisms, not fully clarified, have been proposed to explain how alkylating agents induce retinal ischemia. In particular, thrombosis could be related to the platelet activation mediated by phospholipase A2 increased activity[29].

Paclitaxel was reported to determine symptomatic cystoid macular oedema in a 49-year-old woman with ovarian cancer, probably due to its detrimental effect on the blood-retinal barrier: oedema appeared after more than one year since paclitaxel treatment (cumulative dose of 1,680 mg) and regressed with drug's discontinuation[30]. Chelala and colleagues found an increased central macular thickness, without significant macular oedema nor reduced visual loss, in 25 subjects affected by different solid cancers treated with various protocols (4EC-4T, 3FEC/3T, or 4TC) including paclitaxel or docetaxel[31].

Few reports described retinal damage in paediatric subjects treated with alkylating agents in combination with topoisomerase inhibitors, in particular etoposide[32] [Table 1]. Hilliard and colleagues reported two cases of new-onset blurry vision after 4 months after cisplatin (40 mg/m^2/day) and etoposide (100 mg/m^2/day) initiation. Fundus examination showed a bilateral mild diffuse optic nerve pallor and retinal granular pigmentation[32]. The authors explained the ocular toxicity by the reduced renal clearance of platinum and increased plasma level.

Kwan and colleagues described the case of cisplatin-related retinal toxicity in a 31-year-old male after ten weeks of treatment (20 mg/m^2/day, cumulative dose 528 mg) for testicular cancer[33]: fundus oculi and fluorescein angiographic examinations revealed some cotton wool spots and scattered intraretinal haemorrhages near the macula at both eyes and retinal neovascularization at the left eye. Visual acuity did not improve after laser photocoagulation and the cessation of the chemotherapy[33].

The multidrug chemotherapy regimens usually used for cancer treatment make it difficult to explore the exact role of each drug on the onset of retinal adverse events. In this regard, an interesting report described the case of a 58-year-old diabetic man suffering from bladder cancer who developed, after 4 months of treatment with gemcitabine - antimetabolites molecule - and alkylating agents, microaneurysms, capillary leakage, cotton wool spots, haemorrhages, thickening of the macula, and mild retinal oedema in both eyes[34]. The treatment discontinuation led to an improvement in the retinal injury. However, the cancer relapsed, gemcitabine was reintroduced in monotherapy, and retinopathy appeared again after a month. The clinical improvement observed after gemcitabine withdrawal and the retinopathy relapse after the second exposure to the drug seem to indicate the causal role of gemcitabine in the onset of retinopathy[34].

Higashide and colleagues described the case of a 60-year-old diabetic subject affected by retinopathy and neovascular glaucoma who developed anaemia and cystoid macular oedema during the oral treatment, for advanced gastric cancer, with S-1, consisting of 5-fluorouracil prodrug combined with 5-chloro-2,4-dihydroxypyridine and potassium oxonate (100 mg/day for 48, 26, and 32 consecutive days with an interval of about three weeks)[35]. Macular oedema appeared at the end of the second cycle and regressed three months after S-1 discontinuation. The authors speculated that the retinal hypoxia due to DR worsened for the S-1-induced anaemia, which resulted in the onset of macular oedema, suggesting the need for great attention for the onset or progression of DR in subjects with multiple comorbidities.

Targeted anticancer therapy

Targeted cancer therapies, intended for modulators of specific molecular pathways responsible for the growth and survival of cancer cells, are more specific and less toxic than classical cytotoxic chemotherapy; nevertheless, they could determine adverse effects, including retinal toxicity[18].

The mitogen-activated protein kinase (MAPK) pathway is involved in the regulation of gene expression, mRNA stability and translation, cell proliferation and differentiation, stress response, apoptosis, and survival, thus playing a leading role in oncogenesis[36].

In patients treated with mitogen-activated protein kinase (MEK) inhibitors, the occurrence of ocular adverse events, including asymptomatic to severe disturbances, is reported up to 90%[36] [Table 1]. The term MEKAR (MEK inhibitor-associated retinopathy) describes the retinal adverse events related to the administration of MEK inhibitors, namely retinal vein and central artery occlusion, and separation of the neurosensory retina[36].

Some reports described the occurrence of outer retinal layer separation in subjects treated with selumetinib or pimasertib for astrocytoma and ovarian cancer, respectively. Visual symptoms appeared six months after starting selumetinib and a few days after the administration of pimasertib (60 mg/day), with a spontaneous, without visual sequelae, resolution of the retinal detachment after drugs discontinuation[37,38]. Interestingly, the retreatment with selumetinib determined the relapse of these findings.

Recently, a prospective study involving eight patients treated with pimasertib (60 mg twice a day, continuously for 21 days) for metastatic cutaneous melanoma observed, within the first month after the start of medication, the onset of asymptomatic sub-retinal fluid in all patients, and foveal involvement in six of them[39]. Subretinal fluid spontaneously resolved despite continuation of pimasertib. Diabetes, hypertension, and dyslipidaemia were additional risk factors for more severe events with retinal vein occlusion and visual impairment[36]. Van Djik and colleagues analysed the ocular outcomes of binimetinib in 35 subjects affected by cutaneous or uveal melanoma, treated with 45 mg of oral binimetinib twice a day, continuously for 28 days[40]. Serious retinal events occurred in 77% and 60% of subjects with cutaneous and uveal melanoma, respectively, affecting the fovea in 85% of these cases. These injuries appeared between a few hours to 26 days (median, 14 days) after the start of binimetinib evaluated by OCT. Nevertheless, only 23% of subjects experienced mild and reversible visual symptoms (blurred vision or dark flecks), which generally disappeared within one week despite continuation of the drugs, suggesting that binimetinib discontinuation is not necessary[40].

A retinal involvement related to binimetinib was also reported in a phase one study investigating the efficacy and safety of the molecule in Japanese subjects with solid cancers[41].

The combination of MAPK and BRAF inhibitors, namely trametinib and dabrafenib, determined, in a 39-year-old woman with metastatic melanoma, the onset of multiple serious retinal detachments and severe acute granulomatous panuveitis two weeks after the treatment starting[42]. The recovery of a good visual acuity was obtained after two weeks since drugs discontinuation and corticosteroids administration, although an extensive extra-macula retinal fibrosis remained[42].

The pathogenesis of MEKAR is unclear. There is evidence that the MAPK/MEK pathway regulates tight junctions in retinal epithelial cells, and thus anticancer drugs modulating these pathways could interfere with fluid transport determining retinal oedema[36,37]. Other possible pathogenetic mechanisms include the generation of antibodies against the retinal pigment epithelium cells, found in the serum of subjects treated with binimetinib[40].

Tyrosine-kinase inhibitors (TKIs) are known to increase the risk for renal (asymptomatic albuminuria or nephrotic syndrome) and cardiovascular (hypertension and myocardial ischemia) adverse events[4]. Few studies evaluated the risk of TKIs to determine retinal injury[19] [Table 1]. In particular, imatinib, used in subjects affected by chronic myelogenous lymphoma and gastrointestinal stromal cancers (400-800 mg/day), has been rarely (less than 1% of treated subjects) associated with the onset of retinal haemorrhages and macular oedema, usually resolved after imatinib discontinuation[43,44]. The ocular events mostly occurred in patients treated with high doses of imatinib (600–800 mg/day). Some of these studies also recruited subjects affected by diabetes[44]. Retinal necrosis and oedema were observed in rabbits after the intraocular injection of imatinib[45].

Molecules inhibiting the angiogenesis of cancer cells by targeting the vascular endothelial growth factor (VEGF) signalling are widely used in the treatment of a variety of malignancies. Fraunfelder and colleagues explored the "National Registry of Drug-Induced Ocular Side Effects" to investigate the association between the use of three oral VEGF inhibitors, namely pazopanib, sorafenib, and sunitinib, with the onset of ocular adverse events[46] [Table 1]. Macular oedema or retinal bleeding occlusion and detachments were observed in 15% of the cases after 2-3 months since the drug initiation. The authors assumed that the changes in vascular permeability and the occurrence of microemboli and microvascular events are responsible for the retinal damage. This large number of serious retinal adverse events associated with oral VEGF inhibitors suggests a close monitoring of eye health in treated subjects.

Recent studies reported the retinal side effects associated with fibroblast growth factor receptor 2 inhibitors (FGFR). A multicentre, open-label, single-arm, phase 2 study investigated the efficacy and safety of infigratinib (125 mg/day, orally administered for 21 days of 28-day cycles), a fibroblast growth factor receptor 2 inhibitor, in 108 subjects affected by cholangiocarcinoma. Central serious retinopathy-like and retinal pigment epithelial detachment-like events occurred in 17% of the enrolled subjects. The median time to first onset of ocular side effects was 39 days. No information about the effect of infigratinib on DR is reported[47]. The occurrence of asymptomatic bilateral subretinal fluid, detected on optical coherence tomography scans, was observed in a phase 2 trial of subjects treated with an oral FGFR inhibitor (AZD4547) for malignant pleural mesothelioma[48]. All patients received twice-daily dosing of 80 mg AZD4547 on a nominal 3-weekly cycle. The subretinal fluid emerged between 3 and 19 weeks following the first dose of the drug, did not require any dose interruptions or reductions, and disappeared after the last dose.

In the last decade, therapies targeting the immune response against cancer cells have taken a crucial role in the treatment of metastatic melanoma, non-small-cell lung cancer, renal cell carcinoma, bladder carcinoma,

head and neck cancer, and lymphomas[4]. These medications upregulate the immune system and could determine autoimmune-like side effects in several organs, including the pancreas, thus inducing acute, severe hyperglycaemia with diabetic ketoacidosis observed in 76% of cases[49]. The ocular side effects related to anticancer target therapies occurred, within weeks to months since the beginning of therapy, in approximately 1% of patients[50]. Some reports described the occurrence of optic neuropathy and retinal detachments in subjects treated with ipilimumab (3 mg/kg), a cytotoxic T-lymphocyte 4-antigen antibody. These side effects determined visual disturbances (scotomas or full-field vision loss) and, in subjects who experienced optic neuropathy, improved with corticosteroids or mycophenolate mofetil[50-52] [Table 1]. These features support the hypothesis of an immune-mediated pathogenesis for the development of retinal side effects of cancer immune therapies.

Reedy and colleagues described the case of a 64-year-old woman who developed bilateral vitreous detachment, mild narrowing of the retinal vessels, and retinal thinning after nivolumab administration for metastatic non–small cell lung cancer[52]. Serology testing showed the positivity for antiretinal antibodies against 30-kDa (carbonic anhydrase II), 35-kDa (GADPH), 38-kDA, 58-kDa (PKM2), and 112-kDa proteins. After nivolumab discontinuation and glucocorticoid treatment, the visual symptoms improved[52].

Trastuzumab is a monoclonal antibody used for breast and gastric cancer due to its interference with human epidermal growth factor receptor 2 signalling. Trastuzumab strongly reduces the expression of pro-angiogenic (e.g., vascular endothelial growth factor, transforming growth factor-α, and plasminogen activator inhibitor-1) and is known to induce capillary diameter reduction and leakage[53]. Saleh and colleagues describe the occurrence of bilateral ischemic maculopathy (macular oedema, haemorrhages, and hard exudates), in a 50-year-old woman, three months later the trastuzumab intravenous administration (2 mg/kg)[54] [Table 1]. Thus, the molecule was discontinued for three months and one month after its reintroduction, the visual symptoms worsened again, suggesting its involvement in the retinal damage. Visual impairment was reported in 2% of subjects treated with trastuzumab[54].

CONCLUSION

The current evidence shows that anticancer therapies are associated with different degrees of retinal morbidity ranging from mild transient symptoms to severe, sometimes irreversible, damage. However, the knowledge of the exact pathogenesis of cancer therapies-related retinal damage is limited and inconclusive.

Cancer subjects also affected by T2D could be more prone to develop both short- and long-term retinal adverse effects when treated with cancer therapies, not least because T2D is often associated with other well-known risk factors for retinal damage, namely overweight, hypertension, dyslipidaemia, and metabolic syndrome[10,16]. Anticancer drugs may worsen glycaemic control, thus increasing the risk of retinal worsening. Nevertheless, the exact mechanisms underlying the bad impact of these drugs on glucose levels are unclear and often unpredictable due to the usual administration, in anticancer protocols, of multiple molecules, often supported by glucocorticoids to reduce their side effects[4]. Further mechanistic studies, including cell experiments and animal models, could improve the knowledge of the detailed mechanisms underlying the effects of anticancer drugs on retinal tissue. Pre-registering trials of anticancer molecules reported the retinal side effects, although specific data on the diabetic population are often unavailable.

The management of these subjects is challenging for clinicians due to the lack of guidelines or standardised protocols for the prevention and treatment of retinal damage related to cancer drugs. This review allowed us to identify the anticancer molecules most at risk for retinal neurovascular damage. Nevertheless, other targeted studies are necessary to better clarify how these drugs affect retinal tissues, the exposure time and

dose, the extent and reversibility of symptoms, and the need to discontinue the cancer therapy, the latter representing a difficult choice considering the life-saving role of these treatments. Future research should also address the detection of clinical and easily available predictors of retinal damage in order to carry out, mostly in subjects particularly at risk, a careful retinal evaluation before and after starting cancer therapies. In fact, early diagnosis is essential to prevent the progression of retinal damage and related visual impairment.

The management of these patients is often uncoordinated and too compartmentalised. The clinical complexity and comorbidities of cancer subjects also affected by diabetes make necessary a patient-centred, personalised approach that must involve multiple healthcare professionals organised in a multidisciplinary team (MDT) [Figure 1]. A similar approach, based on periodic, usually weekly, meetings, already exists in medical centres with a huge volume of patients. Oncologists, ophthalmologists, diabetologists, and pharmacologists should work in a coordinated team, sharing intervention strategies, in order to optimise human and economic resources, achieve the best clinical results, and minimize the ocular burden, visual loss, and subject's quality of life impairment.

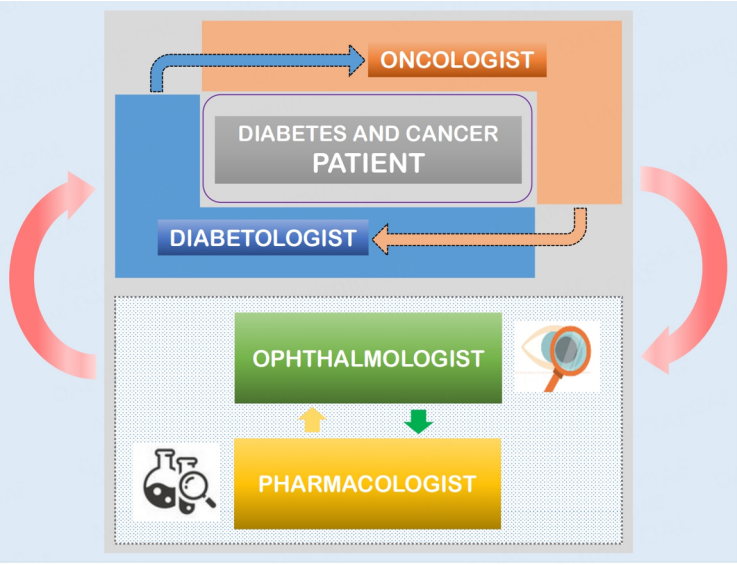

Figure 1. Schematic representation of the network for the prevention and management of retinal adverse outcomes in subjects with diabetes treated with anticancer drugs. Diabetologists and oncologists, the leading figures of the team, collaborate with ophthalmologists and pharmacologists to prevent or treat retinal injury related to cancer therapies, in order to mitigate visual impairment and loss.

DECLARATIONS

Authors' contribution

Conceived the study: Milluzzo A, Sciacca L

Researched references Milluzzo A, Manuella L

Wrote, reviewed/edited the manuscript draft, contributed to manuscript revision, and approved the submitted version: Milluzzo A, Manuella L, Frittitta L, Sciacca L

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Conflicts of interest

Agostino Milluzzo is a Junior Editorial Board Member of the journal *Metabolism and Target Organ Damage*. Other authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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