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Theme Article

Biologics in Oculoplasty

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Abstract

Recent advancements in oncology and immunology have led to the development of biologics, which are newer drugs that target specific molecules involved in tumorigenesis and inflammatory pathways. The current use of targeted therapy has transformed the therapeutic approach for many orbital cancers and inflammatory disorders that were previously treated with conventional treatment modalities. The purpose of this article is to highlight the therapeutic potential of targeted therapy for common orbital cancers and inflammatory conditions.

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Introduction

Recent advances in our understanding of the biological pathways involved in cancers and orbital inflammatory disorders have resulted in the development of agents that act at a specific molecular level, thereby blocking the pathogenesis. Biologics are proteins that have been specifically designed by recombinant DNA technology or monoclonal antibody technology and are used to treat diseases as per the molecular etiopathogenesis.[1] These "molecularly targeted agents"[2] have resulted in a paradigm shift in the management of advanced ocular and periocular malignancies, from "life-sparing" to "eye-sparing" to "vision-sparing" strategies.

Traditional chemotherapeutics and anti-inflammatory drugs have been widely used to reduce ocular morbidity and slow disease progression. However, their action is non-specific, affecting all cells with high mitotic activity and causing significant side effects in other tissues with a high turnover rate. Their long-term use is thus constrained by their potential toxicity and suboptimal outcomes. Targeted treatment interferes with specific molecules implicated in inflammatory or carcinogenic pathways, rather than working against all cells with mitotic turn-over. As a result, systemic adverse effects can be significantly decreased while still delivering precise and effective targeting.

Nomenclature Of Biologics

Monoclonal antibodies and small molecule inhibitors are the two types of chemicals used in targeted therapy.[3] The name of a monoclonal antibody agent ends in -mab, whereas that of small molecule inhibitors ends in -ib.[2] Monoclonal antibodies are developed against specific cell surface antigens and can either block or bind to the cell surface receptor. Blocking the receptor will disable the signaling pathway that would have occurred as a result of natural ligand binding to the receptor. Attachment to the cell surface receptor triggers an antigen-antibody immune response, which leads to cell death.

The name of the monoclonal antibody describes its origin and its specific target molecule. The antecedent mu (-mumab) indicates fully human antibody, zu (-zumab) humanized mouse antibody, xi (-ximab) indicates chimeric or mixed human-animal antibody. The target is indicated by adding -ci(r) for circulatory system, -li(m) for immune system, -t(u) for tumor. For instance, Bevacizumab, an anti-VEGF-A, is a humanized mouse monoclonal antibody (-zumab) acting against VEGF-A of circulatory system (-ci).[3] Antibodies derived entirely or in part from non-human DNA are more likely to cause hypersensitivity reactions and to induce the formation of neutralizing antibodies.

Small molecule inhibitors inhibit a specific metabolic step in the target cell, halting cell growth.[2] The name of the agent indicates the specific enzymatic step blocked. The ending in -tinib is for tyrosine kinase, -zomib for proteasome, -ciclib for cyclin-dependent kinase, -parib for poly-ADP-ribose polymerase inhibitor.[3] For example, imatinib inhibits the Bcr-Abl fusion protein tyrosine kinase, an abnormal protein produced by chronic myeloid leukaemia cells, inhibiting proliferation, and inducing apoptosis.

Biologics In Oculoplasty- Oncologic Conditions

Periocular malignancies pose a management challenge for both functional and cosmetic reasons. Surgery remains the mainstay of treatment for locally aggressive eyelid tumors, with the goal of achieving tumor free margins. Invasion of the orbital septum is considered as orbital extension of the tumor.[4] Orbital invasion of periocular malignancies is one of the most common indications of orbital exenteration.[5] Though a definitive therapeutic treatment, orbital exenteration is a radical, destructive, and cosmetically disfiguring procedure that causes significant psychological trauma to the patient.

Basal cell carcinoma (BCC) is the most common type of malignant eyelid tumor. It is locally aggressive, with a lower predilection to metastasize, and the majority of cases are amenable to wide local excision with tumor-free margins. Advanced inoperable periocular tumors, on the other hand, would result in significantly higher morbidity with surgery.[6] Our recent understanding of the role of abnormalites in Hedgehog signaling pathway in the pathogenesis of BCC and chemotherapeutic resistance has resulted in the development of targeted therapy.[7] The Hedgehog pathway includes the PTCH1 receptor gene, a tumour suppressor gene that has been found to be inhibited in 90% of BCC cases.[4] This deactivating mutation causes overactivation of the Hedgehog signaling via SMO receptor, resulting in cell proliferation and tumorigenesis.[8,9] Vismodegib and sonidegib are anti-SMO therapies that inhibit the downstream activation of Hedgehog signaling pathway.[4] Targeting the Hedgehog pathway could aid in the avoidance

of invasive, cosmetically disfiguring procedures as well as the treatment of inoperable tumors and multifocal BCC like Gorlin syndrome.

Squamous cell carcinoma (SCC) accounts for 5-10% of malignant eyelid tumors.[10] Most cases are managed by wide local excision with or without adjuvant radiation therapy. Studies have reported overexpression of EGFR (epithelial growth factor receptor) receptor in both cutaneous and conjunctival SCC.[11] Erlotinib, a tyrosine kinase inhibitor, is an EGFR inhibitor recently developed for treatment of SCC and has been reported to show efficacy in advanced SCC and candidates ineligible for surgery.[12] It has been proved as a reasonable option for palliative treatment of orbital and cutaneous SCC and significantly improved the quality of life.[13]

The advancement of targeted therapies has resulted in a significant improvement in the prognosis of melanomas. Conjunctival melanomas share characteristics with cutaneous melanomas, such as clinical features, lymphatic metastasis, and a high load of genetic mutations. Surgical excision is followed by a high recurrence rate of 30 to 60%, resulting in lethal metastasis.[14] BRAF, KRAS, NRAF, and NF1 mutations are frequently found in conjunctival and cutaneous melanomas.[15,16,17] Targeted therapy with anti-BRAF and anti-MEK biologics has shown promising results in patients with locally advanced and metastatic melanomas.[18,19] In fact, determining BRAF mutation status is a standard part of the treatment protocol for conjunctival and cutaneous melanomas.[20] In metastatic melanomas that are not amenable to surgery, targeted therapy with checkpoint inhibitors such as pembrolizumab or nivolumab has been found to be beneficial. Checkpoint inhibitors are currently approved against the molecules CTLA4, PD-1, and PDL-1, and they work by blocking the interaction of their target with T-cells, allowing the T-cells to attack the tumor immunologically.[17]

Uveal melanoma is the most common primary intraocular tumor in adults, accounting for about 5% of all malignant melanomas.[21] Standard treatment options include surgical resection, radiation therapy and enucleation. Uveal melanomas differ significantly from cutaneous and conjunctival melanomas in terms of clinical features and course, risk factors, metastasis pattern, genetic mutations, and response to chemotherapy, and thus treatment options for cutaneous melanomas cannot be extrapolated to those for uveal melanomas. In comparison to cutaneous and conjunctival melanomas, uveal melanomas have a lower number of genetic mutations and a worse prognosis, with life expectancy significantly reduced in the event of metastasis.[17] There is currently no approved targeted therapy for uveal melanomas, but clinical trials with the tyrosine kinase inhibitor sunitinib (c-KIT, CD117) and anti-receptor tyrosine kinase crizotinib (crizotinib) are ongoing (ROS-1, ALK).[17]
Sebaceous gland carcinoma (SGC) of eyelid is a rare periocular malignancy, managed by surgical wide local excision with tumor free margins. The use of targeted therapy in SGC of eyelid has not yet been reported, but a recent study has reported the upregulation of Hedgehog pathway.[22] Anti-SMO molecules as in BCC can come into play as targeted therapy. Studies have also reported the involvement of the HER2 and Pi3K signalling pathways in SGC and are potential targets for further clinical studies.[23,24]

Biologics In Oculoplasty- Orbital Inflammatory Conditions

Commonly encountered orbital inflammatory conditions include thyroid eye disease (TED), dacryoadenitis, myositis, cellulitis. They present with a variety of clinical manifestations, the most common of which are periorbital swelling and pain. The standard treatment regimen includes systemic corticosteroids, as well as immunosuppressants such as alkylating agents, antimetabolites, cytotoxic drugs, calcineurin inhibitors, lymphocyte inhibitors, and tumor necrosis factor-α inhibitors. However, suboptimal response and toxicity with prolonged use of immunosuppressants has prompted the development of alternate treatment options targeting the abnormal biochemical pathways.

Thyroid eye disease is one of the most common causes of orbital inflammation, and several monoclonal antibodies have been developed to treat it. Rituximab (RTX), a well-known lymphoma treatment, is an anti-CD20 monoclonal antibody that targets CD20 on B-cells, the cells that produce antibodies. It works in TED by decreasing TSH-receptor antibodies, which reduces inflammation and TED activity. Its role in compressive optic neuropathy is debatable due to the possibility of edema and orbit volume expansion caused by massive B-cell lysis.[25] TNF-α inhibitors, which were originally used to treat cancer, are now being used as pleiotropic cytokines in immune and inflammatory responses by regulating apoptosis and cell survival.[26] They work by inducing cellular toxicity in TNF-α overexpressing cells via antibody-dependent and complement-dependent mechanisms.[27] These drugs, which include infliximab, adalimumab, etanercept, golimumab, and certolizumab, have been shown to be effective in reducing soft tissue signs and compressive optic neuropathy.

Tocilizumab is an interleukin-6 (IL-6) receptor antagonist that has recently been discovered to be an effective biologic in the treatment of orbital inflammatory disorders. IL-6 is a pro-inflammatory cytokine that activates T-cells and promotes immunoglobulin production, and it is found in high concentrations in thyroid eye disease.[28] Tocilizumab works by blocking IL-6 receptors and has been shown to improve clinical activity scores in refractory cases. Teprotumumab is the most promising drug for thyroid eye disease, and it has been recently approved by the FDA. It is an antibody that binds to IGF-1 (insulin-like growth factor-1) receptors and prevents thyroid stimulating hormone from activating proinflammatory cytokines.[2] It is the only medication that has been shown to improve clinical activity and proptosis while also providing a consistent response.[29] Its main advantage over other biologics is a significant improvement in proptosis. Though there is insufficient data on clinical

trials of biologics in thyroid eye disease, these drugs appear to be a promising tool for improving the quality of life in these patients.

Rituximab is being used successfully as an adjunct to steroids and radiation therapy as well as a steroid-sparing agent in other orbital inflammations such as IgG4 disease, idiopathic orbital inflammation, granulomatosis polyangiitis, and mucous membrane pemphigoid. TNF-α inhibitors, particularly infliximab, are being reserved for recalcitrant and recurrent cases of idiopathic orbital inflammation, as well as IgG4 disease.[30-32]

Commonly Encountered Side Effects With Biologics

A number of side effects have been reported with the use of biologics in the orbit, eyelid and lacrimal system. When used for metastatic melanomas, BRAF inhibitors such as vemurafenib and sorafenib have been linked to cutaneous squamous cell carcinomas and keratoacanthomas.[33] The EGFR receptor is involved in the normal development and differentiation of hair follicles, and its inhibition can result in abnormal hair growth. EGFR inhibitors, which are used to treat squamous cell carcinomas, can cause blepharitis, Meibomian gland dysfunction, dry eye, hypertrichosis and poliosis.[34] Imatinib, a tyrosine kinase inhibitor has been reported to cause periorbital edema, chemosis, blockage of lacrimal drainage.[35] EGFR and VEGF inhibitors have been shown to slow wound healing, and ibrutinib has been shown to interfere with coagulation.[2] Checkpoint inhibitors can increase post-operative inflammation and are more likely to cause post-operative infection.[2] Thus, prior to planning surgery for patients who are already receiving targeted therapy, a thorough discussion with the oncologist should be held.

Conclusion

The use of biologics has resulted in a paradigm shift in the treatment of orbital, lacrimal, and eyelid oncology and immunology. The widespread use and innovation of these agents emphasises the importance of understanding the molecular basis of etiopathogenesis of the disorders in order to develop targeted rational therapeutic approaches. There is still a lack of data on prospective, randomised studies on targeted agents, which should be the next goal in the near future. This can aid in understanding the validity of their long-term efficacy, outcomes and adverse effects.

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