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Review

Neuroblastoma-targeted Anticancer Drug Delivery

Nöroblastomda Hedeflenmiş Anti Kanser İlaç Taşınımı

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ABSTRACT

Neuroblastoma (NB) is the most common solid tumor in pediatric cases. NB accounts for about 8% of malignancies in patients younger than 15 years, and since 50% of newly diagnosed cases metastasize to regional lymph nodes, bone marrow, bone, liver, and skin, the disease is usually diagnosed in its late stages. Overexpression of N-MYC, which is characterized by poor prognosis in NB, changes the progression of the disease and the course of the treatment. Targeting these pathways may be a treatment option in NB, since the mTOR and AURKA pathways interact with N-MYC and directly cause protein stabilization. The widespread use of conventional chemotherapeutics has some limitations associated with their common side effects and the bioavailability of the drugs. New therapeutic approaches have focused on nanoparticle (NP) -based therapies, and chemoimmunoagents in the form of many NPs are being tried in NB. Here, we review new therapeutic approaches that would help to treat NB.

Keywords: *Neuroblastoma, nanoparticle, signaling pathways*

ÖZ

Nöroblastom (NB), pediatrik olgularda en yaygın görülen solid tümördür. NB, 15 yaşından genç pediatrik hastaların %8'inde malignansi göstermekle birlikte, tanı konanlarda %50'sinde bölgesel lenf noduna, kemik iliğine, kemiğe, karaciğere ve deriye metastaz görülmektedir. Hastalık genelde geç evrelerde tanı almaktadır. N-MYC'nin aşırı ekspresyonu NB'de kötü prognoz ile karakterize olmuştur ve tedavi ve hastalığın ilerleyişini değiştirmektedir. mTOR ve AURKA yolakları N-MYC ile ilişkili olarak protein stabilizasyonuna neden olduğundan dolayı, NB'de bu yolakları hedeflemek yeni bir tedavi stratejisi oluşturabilir. Günümüzde kullanım alanı geniş olan konvansiyonel kemoterapötik ilaçlar, bilinen yaygın yan etkileri ve ilacın biyoyararlanımı gibi sebeplerden dolayı bazı sınırlayıcı faktörlere sahiptir. Yeni terapötik ajanlar, nanopartikül (NP) bazlı tedavilere yönelmiştir ve NP formunda birçok kemoimmünoajan NB'de denenmektedir. Bu makalede NB tedavisinde kullanılan yeni yaklaşımları özetledik.

Anahtar kelimeler: *Nöroblastom, hedeflendirilmiş tedavi, nanopartikül*

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INTRODUCTION

Neuroblastoma (NB) is an embryonic tumor originating from the neural crest. The best defined genetic change in NB is the overexpression of the MYCN protein, which occurs in approximately 20% of all NB cases and is associated with its high-risk phenotype. Although targeting MYCN is quite challenging due to the lack of suitable surfaces on the DNA binding domain to which drugs can bind, indirect targeting method has been shown to be the most effective approach to inhibit or control the regulation of MYCN. Overexpression of Myc dramatically changes the trajectories of gene expression. Everolimus, a hydroxyl ester of rapamycin, is an agent specific to the mTOR pathway and inhibits the nuclear pathway. AURKA is critical for the assembly and stability of mitotic spindle strands, as well as the regulation of centrosome and kinetochore formation. It stabilizes MYCN by direct protein-protein interaction, making it less degradable by the nuclear proteosome complex [(1)].

Although inhibition of Myc is an FDA-approved therapeutic strategy, the development of clinical compounds that directly target proteins (IDPs) is disrupted by natural mutations, such as Myc, and lack of stable and well-defined molecular packings probed with small molecules has created new therapeutic challenges. Conventional chemotherapeutics, although toxic to cancer cells,

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also damage healthy cells. Encapsulating drugs in nano-carrier systems targeting cancer cells is an effective method in presenting drugs in combinations and reducing toxicity. Hybrid lipid-polymer nanoformulations combine the advantages of both models, providing controlled drug release and enhanced bio-functionality. In recent studies, it has been shown that nanoformulations, which are being studied as a new therapeutic method, provide advantages in drug delivery and imaging in many molecular cancer therapies and conventional chemotherapy.

Neuroblastoma

Neuroblastoma (NB) is a pediatric solid tumor involving the sympathetic nervous system. The incidence rate of NB in children <15 years of age is 1.2 cases per 100,000 and accounts for approximately 15% of cancer-related pediatric deaths. The clinical picture and outcomes of NB are highly heterogeneous, due to disease regression, its multifocality and multidrug resistance [1]. N-MYC amplification has been reported in approximately 25% of NB cases, and N-MYC amplification has been considered the strongest marker associated with a poor prognosis and rapid progression of the tumor in approximately 40% of high-risk patients. Other anomalies seen in NB are loss of 1p heterogeneity (30%), 11q deletions (45%) and 17q gains (60%) which are associated with diploid or tetraploid karyotypes. In addition, ALK amplification encoding anaplastic lymphoma kinase (ALK) receptor tyrosine kinase is seen in 1-2% of the cases and has been mostly evaluated together with N-MYC amplification. Recently, a large genomic rearrangement known as chromotripsis has been observed in 18% of advanced stage tumors; Therefore, NB can be considered a type of cancer that is predominantly dependent on copy number. Approximately 8-10% of sporadic NB tumors are seen with point mutations in ALK. In addition, 1-2% of NB tumors show ALK amplification that actually occurs only in the presence of N-MYC amplification, given their proximal association on chromosome 2p23-24. Therefore, ALK amplification is also a predictive marker of poor prognosis. ALK variants serve as important biomarkers in NB, as they confer sensitivity to small molecule kinase inhibitors currently under clinical evaluation in phase I and II trials [2].

Current Treatment Approaches in Neuroblastoma

The treatment algorithm for NB depends on the risk stratification defined using parameters such as age, disease stage, tumor histopathology, coefficient of MYCN amplification and DNA ploidy. Since spontaneous regression is often observed in this risk group, low-risk patients are usually evaluated only intraoperatively or with close follow-up. In contrast, intermediate-risk patients need both surgery and chemotherapy. High-risk patients are treated with high-intensity chemotherapy, radiotherapy, surgery and autologous hematopoietic stem cell transplantation. In addition, high-risk patients receive immunotherapy with anti-GD2 antibodies and cytokines, and differentiation therapy with 13-cis-retinoic acid to eliminate minimal residual disease (MRD) [2]. NB contains a large number of genetic and protein aberrations. Most of the potential therapeutic targets for NB have been evaluated in preclinical studies. Since epigenetic factors also contribute to the disease, in addition to targeting signaling pathways, and treatments with tyrosine kinase inhibitors, several agents also target epigenetic regions. DNA methyltransferases (DNMTs), enzymes responsible for histone modifications (acetylation, methylation and deacetylation), can be also targeted [3].

The anti-GD2 monoclonal antibody dinutuximab (Unituxin) is the first treatment approved by the Food and Drug Administration (FDA) in the treatment of a high-risk NB. Multiple immunotherapy strategies continue to be developed for the treatment of NB and may have a place in the treatment of relapsed high-risk NB disease [4].

Aurora Kinases

Aurora kinases belong to a small family of proteins

made up of triple serine-threonine kinases (Aurora A, B and C). They are very important molecules for the stage of mitosis, as they play a role in the maturation of centrosomes, separation of chromosomes and cytokinesis. Aurora kinases play a role in the initiation and progression of many tumorigenic processes by dysregulating the phosphorylation of H3, a histone protein, and tumor suppressor p53. They are overexpressed in many human tumors, including 50% of colorectal, ovarian, and stomach cancers. With the overexpression of aurora kinases, multiple centrosomes and multipolar spindle filaments are formed in the cell. Thus, genetic instability occurs, which contributes to tumor formation [3].

In humans, the aurora kinase family consists of 3 members; Aurora A, B, and C. Each of these shares a conserved C-terminal catalytic domain but differ in their intracellular localization, substrate specificity, and functions during mitosis. Aurora A binds to TPX2 at the start of mitosis and is activated by autophosphorylation at threonine 288 (T288). Immediately after its activation, Aurora A phosphorylates multiple substrates that regulate centrosome maturation and mitotic spindle strands. Aurora B is part of the chromosomal passenger complex (CPC) together with the centromere protein, survivin and borealin. Aurora B is activated through binding and phosphorylation of the centromere protein in a positive feedback mechanism. Since phosphorylation of histone H3 by Aurora B at serine 10 (S10) and serine 28 (S28) is required for condensation of the chromosome, inhibition of S10 phosphorylation is widely used as a biomarker for Aurora B inhibition in vitro and in vivo settings. Aurora C also plays a role in chromosomal structure like Aurora B, but its expression site is limited to the testicles [4].

AURKA gene encodes Aurora kinase enzymes. It has been shown that AURKA is widely overexpressed in various tumors, including NB. Overexpression of AURKA has been associated with a poor prognosis. In addition, overexpression of AURKA is closely related to overexpression of MYCN. Studies have shown that AURKA can form a complex with MYCN to stabilize the MYCN structure and prevent its degradation, while inhibition of AURKA activity can promote the disruption of the stabilization of MYCN. Thus, targeting AURKA therapeutics not only improves the effect of NB therapy by inhibiting the activity of AURKA, but also achieves the goal of lowering the expression levels of the MYCN protein [5].

An agent named MLN8237 (alisertib), an Aurora Kinase A inhibitor, has been studied in preclinical models and in phase-I of relapsed/refractory solid tumors. In studies using single and double doses, dose-limiting toxicities stemming from mucositis and myelosuppression were noted with double dosing. Recommended dosage for Phase-II has been found to be 80 mg/m^2/day. Although the response rate seems low when used as a single agent, based on preclinical data, MLN8237 works synergistically with irinotecan and temozolomide and therefore this combination is studied in relapsed or refractory cases. This is a significant combination with an overall response rate of 31.8% in phase 1 trials, but currently the use of this agent in NB has not been investigated in any ongoing study [6].

Thus, instead of targeting Aurora A alone, the use and combination of pan-Aurora inhibitors can provide a more comprehensive antitumor effect. The potent activity of Tozasertib (VX680,MK-0457), a pan-Aurora inhibitor, has been revealed in drug-resistant NB cell lines The findings, supported by the studies conducted, reveal that Aurora inhibitors are effective as monotherapy or in combinations with other agents, in the stabilization and post-translational inhibition of N-MYC. Anti-tumor effects have also been tested in in vivo NB models. While inducing permanent tumor regression in multiple tumor xenograft models, even more significant results have been observed with anti-tubule chemotherapeutics [7].

PI3K / AKT / mTOR Pathway

Abnormal activation of the PI3K/AKT/mTOR pathway has been demonstrated in NB which plays an important role in stabilization of N-MYC. The mTOR signaling pathway is critical for cell growth, proliferation and survival. It is also known to have a

central role in a signaling pathway consisting of many components involved in tumorigenesis including mTOR, PI3K, AKT, PTEN, TSC1/TSC2, p53, LKB1 and downstream proteins S6K1, eIF4E, FOXO. Many studies have revealed that the genetic regulation of mTOR may also play an antitumor role in pediatric NB through upregulation of tumor suppressor proteins PTEN, FOXO, TSC1/TSC2, p53 and LKB1 or downregulation of oncogenes in the pathway [8].

Phosphorylation (55.2%) of the S6 ribosomal protein, which is the target of mTOR, was observed in NB samples [8]. This evidence of mTOR activity in cellular processes that contribute to the development and progression of NB has established mTOR as the main link in tumorigenesis in NB.

Preclinical data support the essential role of mTOR in cancer; Thus, agents targeting the activity of key proteins in the mTOR signaling pathway could be a potential therapeutic method in the treatment of NB. As a result, mTOR inhibitors, mTOR kinase inhibitors, and inhibitors of mTOR regulators have been developed and evaluated for their safety and efficacy in patients with cancer, including NB. Analogues targeting mTOR, including rapamycin, temsirolimus, everolimus, and ridaforolimus, affect mTORC1 with a similar mechanism of action [9,10].

A New Treatment Perspective with Drug Delivery Systems in NB

Drug delivery systems have long been studied as a way of delivering cytotoxic chemotherapy directly to a tumor or other site of action, while potentially reducing systemic side effects [11]. Nanodrug delivery systems provide promising strategies for cancer chemoimmunotherapy because they are easily internalized by cells of the immune system and can rearrange the tumor microenvironment due to their specific physical and chemical properties, thereby reinforcing the immune system. These systems can maximize the solubility of the chemotherapeutic agents used and their bioavailability to the body, prolong the circulation time of the agents in the body with passive or active targeting, increase the accumulation of agents in tumor tissue, and improve in vivo pharmacokinetic behavior, leading to increased therapeutic effects and decreased side effects [12].

In drug delivery systems applied in chemoimmunotherapy, basically several approaches exist for delivering more than one agent to the target tissue in combination. If more than one agent is to be administered in combination, one agent can be administered in free form and the others can be administered with a drug (Free Drug + Nano) absorbed in the nanoparticle (NP) or both can be administered with similar or different NP (Nano + Nano) or both agents are co-encapsulated (co-encapsulation). “Free drug + Nano” approach is one of the most up-to-date approaches in the current treatment of cancer in nanomedicine. “Free drug + Nano” approach has shown favourable properties such as adjustable dose, controllable application range, easy preparation, facilitated industrial preparation and clinical orientation. These approaches basically involve two strategies. The first is that the immunotherapeutic agent can be administered in appropriate NPs and the chemotherapeutic drug is administered in its free form. Yong Taik Lim et al. [13] designed two poly lactic-co-glycolic acid (PLGA) NPs combined with a chemotherapeutic agent, paclitaxel (PTX). One of them is CpG- loaded PLGA-NPs (PCNs), the other is PLGA NPs (PINs) loaded with IL-10 miRNA designed primarily to suppress IL-10. In this study by Yong Taik Lim et al, it was found that PTX treatment followed by PCNs and PINs can increase the antitumor effect

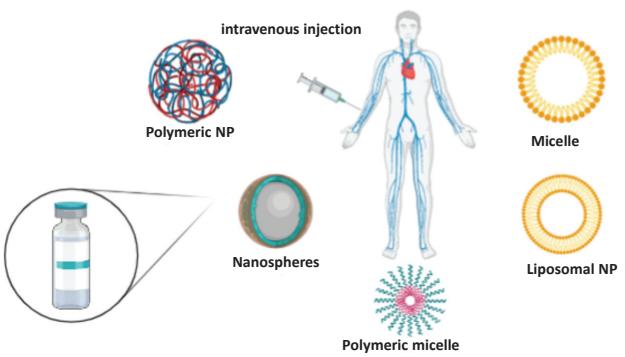


Figure 1. The most commonly used NPs in cancer immunotherapy and intravenous administration.
It is designed in the BioRender application.

and survival rate of the chemotherapeutics used in murine melanoma models carrying B16 F10 compared to PTX alone ($p<0.05$). Another "Free drug + Nano" approach is designed to give the immunotherapeutic agent in its free form and to load the chemotheraprutic drug onto the NP. The "Nano + Nano" approach can be flexible in the design and formulation of NPs. Besides, the application dosage can be adjusted and the coordinated distribution of the two agents can be realized [14].

Engineered NPs can be in different forms. Of these; chitosan is a natural carbohydrate polymer Derived from deacetylation of chitin, it is considered suitable for pharmaceutical applications due to its low price, high biocompatibility, low toxicity and ability to be degraded by chitinases in the body. During the production of chitosan-based NPs, toxic organic solvents or heat are not needed and they can be dissolved in acidic aqueous solutions. Small molecules, proteins and polynucleotides can be added to chitosan/NP. Chitosan can release the encapsulated drug in a controlled manner. Silica xerogels are in the class of inorganic molecules used in drug transport. They are biocompatible and also easily modifiable. Polylactide-co-glycolic acid (PLGA) is a copolymer of polylactic acid (PLA) and polyglycolic acid (PGA) is synthesized by ring-opening polymerization of lactide (LA) and glycolide (GA). The use of PLGA in drug transport in biomaterials provides many advantages. First, it has already been approved by the US Food and Drug Administration (FDA) and the European Medical Agency (EMA) for use in the human body. Also, as a synthetic polymer, it has higher purity, suitable molecular weight, and higher reproducibility than many natural polymers. In addition, PLGA is biodegradable, when it undergoes hydrolytic cleavage in the body. It is reduced to lactic acid and glycolic acid and metabolized through the Krebs cycle into CO_2 and water. Compared to PLA and PGA, the copolymer is more stable to hydrolysis and can therefore be used for drug release that lasts for days, weeks or months [14].

Polymer micelles are thermodynamically stable colloidal solutions formed by combining amphiphilic block copolymers. Drugs in the form of hydrophobic small molecules can be encapsulated in the hydrophobic core of micelles. In addition, hydrophilic drugs can be loaded onto the NP through physical interactions or chemical conjugation. Paclitaxel loaded with Genexol® and docetaxel loaded with Nanoxel (DTX) are NPs approved for cancer treatment. Polymer micelles are widely used in cancer chemoimmunotherapy. Dendrimer NPs are hyperbranched spherical polymers composed of a hydrophobic central core, branched monomer, and functional peripheral groups. Small molecular drugs can be loaded onto the nucleus. In addition, the functional peripheral group in the dendrimer chemically binds immunotherapeutic agents such as therapeutic antibodies. Currently, commonly used dendrimers are polyamidoamine (PAMAM), polypropyleneimine (PEI) and peptide dendrimers [12].

Nanogels are another structure in which chemotherapeutic agents are frequently loaded. Nanogels containing a nano-sized hydrogel scaffold are biocompatible and have a high water content. They are compatible with a variety of therapeutic agents and considered as promising toosl in chemoimmunotherapy [14].

Treatment Strategies with NB Targeted NPs and Using Nano-Technology

Drug delivery strategies play an important role in the treatment of NB. Being able to deliver the drug more effectively, earlier and with a longer-lasting effect can be an effective role in preventing the disease. Today, in liposomal systems, which are one of the most important drug delivery systems, different applicable liposomal drug delivery strategies for NB treatment are available All contain a drug or compound encapsulated in a liposome embellished with different molecules or ions capable of targeting a particular molecule on or in the NB.

Apart from liposomal systems, CNTs, drug loaded silk films, amphiphilic diblock polymers and different types of NPs, especially PEGylated PLGA co-polymers, can be engineered by targeting ligands common in the NB and drug delivery, which can efficiently

deliver the chemotherapeutic agent to the target site. systems. Different drug transport systems have been tried in NB. Among these trials in a study on encapsulation of siRNAs, it was aimed to encapsulate MYCN siRNA in a liposome coated with folate molecules. As it is known, overexpression of MYCN is associated with poor prognosis in NB. Therefore, a specific siRNA has been used to silence this gene to a certain extent. Folate is a low- weight molecule that is highly absorbed by tumor cells to aid in division compared to normal cells.

In this case, due to the surface conjugation of the engineered NPs with folate, the tumor can enter more easily through overexpressed folate receptors. With this method, researchers have been more successful in silencing MYCN and apoptosis and have shown that this is an effective method for drug transport in NB. TNF-α is an inflammatory cytokine that can affect vascular permeability and angiogenesis. With this feature, a treatment strategy has been developed by targeting TNF-α in drug loaded nano liposomes to be used before chemotherapy.

CD13 is highly expressed in NB. The NGR peptide is a suitable ligand for CD13 targeting tumor vascularization. Studies have shown that the combination of TNF - α and NGR can cross the barriers to drugs, access into the tumor and help deliver a higher drug concentration to the tumor. Therefore, designing a nano-liposome targeting CD13 by NGR containing a chemotherapeutic agent (eg doxorubicin) would result in better drug delivery and greater drug uptake. GD2 is expressed in neural crest-derived tumors and peripheral nerve cancer cells, and targeting this molecule with antibodies so as to deliver drugs to the target more effectively has been the subject of recently performed studies.

Coating liposomes with hydrophilic agents reduces cellular drug uptake outside the target sites, slows down the escape from the immune system, and decreases the total drug dose needed, resulting in a higher level of free drug in the bloodstream compared to the conventional drug delivery systems. Therefore, the strategy to engineer a nano - immunoliposome, typically 10-200 nm in diameter, that encapsulates the chemotherapeutic drug, coated with a hydrophilic agent such as polyethylene glycol (PEG), and decorated with an antibody against a tumor target such as anti-GD2, has high efficacy in the treatment of NB, and can be considered as an effective complex [15].

Inhibitory agents specific to mTOR and Aurora pathways, which are directly related to the N-MYC pathway and are involved in N-MYC stabilization, can be targeted to GD2, an antigen receptor on the surface of the NB cell, with PEGylated co-polymers. Although there is information in the literature regarding the use of both agents together in different cancer types, there is no study conducted in NB [16].

CONCLUSION

Apart from all the results obtained in NB treatment, based on clinical and preclinical knowledge, treatment of neuroblastoma is managed by combined use of chemotherapy and immunotherapy. Molecules used in immunotherapy are being combined with drugs used in conventional chemotherapy. It is anticipated that combined use of agents will maximize the anti-tumor effects of the agents via a synergistic mechanism. Nano-carriers are being used with the aim to increase the effectiveness of the agents used in targeted NB treatment strategies. Chemotherapeutic and chemoimmunotherapeutic agents loaded onto NPs created by using many molecules have positive effects such as increasing solubility of the drugs and prolonging their bioavailability in the body. This treatment strategy has also several advantages as increased circulation time in the body, targeting to a specific site, and improved pharmacokinetic behavior of the drug.

All of these treatment strategies are critical to improving outcomes in high-risk NB patients. Research areas in rapidly expanding cancer genomics, immunotherapy fields, nano-carriers and targeting with nano-technological molecules are promising possibilities for the future treatment of NB.

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