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Novel Targeted Therapies for Inoperable Plexiform Neurofibromas in Neurofibromatosis Type 1 Patients: A Review

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ABSTRACT

Neurofibromatosis Type 1 (NF1) is a common autosomal dominant disorder characterized by neurofibromas, café-au-lait spots, and other manifestations. A significant challenge in NF1 management is the presence of plexiform neurofibromas (PNs), benign but often debilitating tumors affecting about 20% of children with NF1. PNs can cause severe pain, motor dysfunction, and even transform into aggressive malignant peripheral nerve sheath tumors (MPNSTs), which have high morbidity and mortality. Surgical resection is the primary treatment for accessible PNs; however, many are inoperable due to their diffuse nature or proximity to vital structures.

The pathogenesis of PNs is complex, rooted in mutations of the NF1 gene (17q11.2), which encodes neurofibromin, a protein crucial for regulating cell growth via the RAS-MAPK pathway. Loss of functional neurofibromin leads to constitutive activation of this pathway, promoting uncontrolled cell proliferation. The tumor microenvironment, particularly the presence of mast cells and their interaction with Schwann cells and fibroblasts, also plays a critical role in PN growth and vascularization.

Traditional systemic therapies like chemotherapy and radiation have shown limited efficacy for MPNSTs and are often associated with risks for PN patients, especially children, due to concerns about secondary malignancies and vasculopathy. This underscores the critical need for targeted therapies.

A significant therapeutic shift occurred with the development of MEK inhibitors. Selumetinib was the first FDA-approved medical treatment for pediatric NF1-associated inoperable PNs, demonstrating significant tumor shrinkage and durable responses in clinical trials. More recently, mirdametinib has emerged as a promising MEK1/2 inhibitor. Clinical trials show mirdametinib's efficacy in both adults and children, achieving substantial tumor volume reduction in a shorter timeframe with a favorable safety profile. Notably, mirdametinib's ability to cross the blood-brain barrier makes it beneficial for associated gliomas, and its lack of interaction with cytochrome P450 enzymes minimizes drug interaction concerns. Its availability in multiple formulations further enhances patient compliance. These advancements, coupled with improved 3D MRI analysis and standardized outcome measures from the REiNS collaboration, are revolutionizing the management of inoperable PNs, offering new hope for improved patient outcomes and quality of life.

1. Introduction

Neurofibromatosis (NF) refers to a group of genetic conditions involving the development of tumours that may affect the brain, spinal cord, and the nerves [1]. There are three types of NF-Type 1 also known as Recklinghausen disease, NF Type 2 and schwannomatosis. The prevalence of NF1 globally is 1 in 3,000-4,000 births and NF2 is 1 in 50,000-60,000 births.NF1 symptoms arise from neural crest-derived tissue (e.g. glia, Schwann cells, melanocytes), some reports have characterized NF1 as a disorder of the neural crest. NF type 1 and type 2 treatment includes clinical monitoring and medical intervention when appropriate [2].

1.1 Neurofibromatosis Type 1 (NF1) and its Clinical Manifestations

Neurofibromatosis type is an autosomal dominant disorder presenting with multiple cutaneous and non-cutaneous manifestations. It is caused by *loss of function mutation in NF1 gene* located on 17q11.2 chromosome and codes for *neurofibromin.* Neurofibromin plays an important role in cell growth, survival and cell division regulation. Most of the NF1 cases are diagnosed in early childhood and have average life expectancy. Manifestations of NF1 are- Freckling of skin in axilla/groin region, Neurofibroma, Cafe au lait spot, Scoliosis, long bone dysplasia, attention deficit hyperactivity disorder (ADHD),lisch nodules in eye[3].

Evaluation

NIH has 7 diagnostic criteria's for NF type. To label a case of NF1 there should be ≥ 2 criterias from the 7 diagnostic criteria's given[3]:

1.Six or more cafe-au-lait spots greater than 5 mm prepubertal and greater than 15 mm post-pubertal

2.Two or more neurofibromas or one or more plexiform **neurofibroma**

3.Axillary or groin freckling

4.Optic glioma

5.Two or more Lisch nodules

6.Sphenoid dysplasia, dysplasia or thinning of long bone cortex

7.First-degree relative with **neurofibromatosis** type 1

1.2 Plexiform Neurofibromas (PNs): Burden and Challenges

Plexiform neurofibromas (PNs) are benign, networked peripheral nerve and fibroblast tumors affecting about 20% of children with NF1. Complications include pain, motor dysfunction, and weakness. PNs can become life-threatening if they transform into malignant peripheral nerve sheath tumors. While surgical resection is the definitive cure, unresectable PNs (e.g., those near vessels) rely on medication to reduce tumor volume [4].

1.3 The Need for Targeted Therapies for Inoperable PNs

NF1-Plexiform Neurofibromas (PNs) can cause new or persistent symptoms in adolescents and adults, potentially worsening with untreated tumor growth. Though typically benign, PNs rarely turn malignant. As NF1 is a lifelong condition, its symptoms and impact on quality of life can change throughout a person's life. [5]. However, initial studies with imatinib [6] ,tipifarnib[7], pirfenidone[8], sirolimus [9][10] and interferon alfa-2b[11] only achieved marginal benefits. The therapeutic revolution came in 2020 with the development of the MEK inhibitor (MEKi) **Selumetinib** as the first effective medical targeted therapy for PN[5].

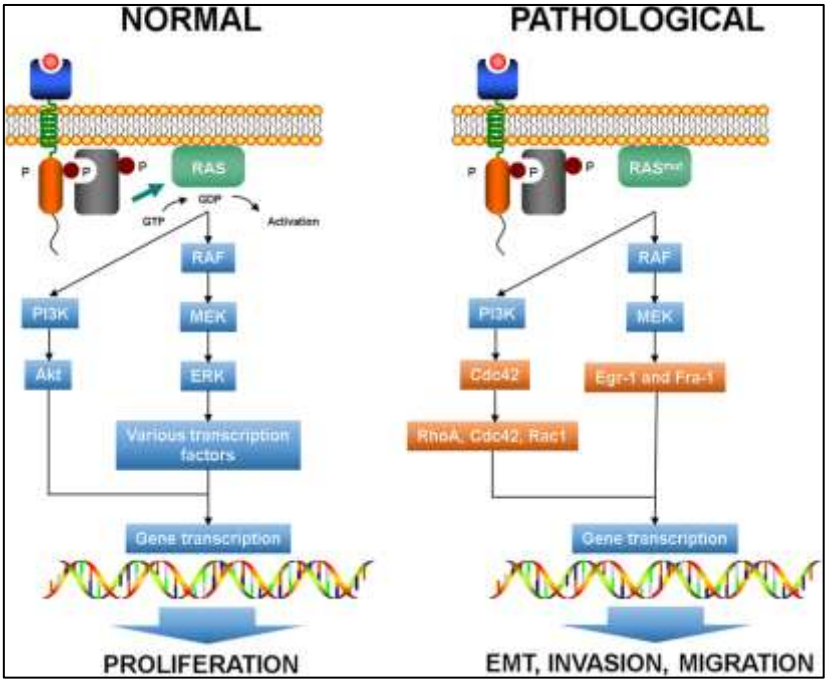
2. Understanding the Pathogenesis of Plexiform Neurofibromas

Plexiform neurofibromas (PNs) cause lifelong disfigurement, disability, and can even be fatal. Their growth is supported by mast cells, which promote fibroblast expansion and collagen synthesis, and by Schwann cells and fibroblasts that directly contribute to blood vessel formation. PNs often compress cranial nerves or spinal nerve roots, leading to a range of severe issues like paresthesia, paralysis, drooling, sleep disturbances, respiratory and gastrointestinal problems, blindness, and loss of bladder/bowel control. A significant concern is their potential to transform into malignant peripheral nerve sheath tumors (MPNSTs), a highly aggressive and metastatic cancer affecting up to 10% of NF1 patients. Research using NF1 knockout mice (Nf1+/n31), which mimic human NF1 mutations by having reduced neurofibromin protein levels, helps in understanding this complex disease. [12].

2.1 The Role of the NF1 Gene and Neurofibromin

Neurofibromatosis type 1 (NF1) results from mutations in the NF1 gene (17q11.2 locus), which encodes neurofibromin, a large (2818 amino acids, 250-280 kDa) protein crucial for nervous system function (neurons, Schwann cells, oligodendrocytes) and found in the adrenal medulla, leukocytes, and testis. Neurofibromin negatively regulates the RAS-cyclic AMP pathway, showing homology to *Saccharomyces cerevisiae* IRA1/IRA2 genes. Human neurofibromin's amino acid sequence exhibits high conservation: 98.5% identical to rat, 99.4% to dog, 100% to chimpanzee, gorilla, orangutan, gibbon, and marmoset, 96% to rhesus macaque, and 83% to mouse lemur, highlighting strong evolutionary selective pressure on its structure and function. [13,14]

2.2 Aberrant Signalling Pathways in PN Development



The discovery and cloning of the NF1 gene were critical for NF1 diagnosis and understanding its pathology. Roughly half of human NF1 mutations are spontaneous, typically leading to truncated neurofibromin. Post-meiotic mutations can result in segmental NF1, where manifestations are localized or limited to specific cell types (e.g., pigmentation issues only). While most NF1 frameshift and point mutations don't directly correlate with disease severity, microdeletions of the entire NF1 locus (under 10% of mutations) are linked to earlier onset and more severe disease. [12]. **Nf1 traditional knockout** - Nf1 knockout mice harbor a disruptive neomycin cassette in Nf1 exon 31 (Nf1+/n31), an exon site homologous to a "hotspot" of human NF1 mutations. The encoded neo cassette induces protein instability and degradation, leading to an approximate 50% reduction in total neurofibromin protein level [12].

2.2.1 RAS(Rat sarcoma)/MAPK (Mitogen activated protein kinase) Pathway

The RAF/MEK/ERK pathway is a crucial MAPK signaling cascade controlling cell development, differentiation, proliferation, and death. Its dysregulation, frequently due to RAS mutations found in ~30% of cancers, causes constitutive activation, leading to uncontrolled cell growth and drug resistance. Specific RAS mutations are associated with distinct cancers (e.g., NRAS in lymphoid/myeloid, KRAS in colon/pancreatic, HRAS in bladder/kidney). MAPKs are Ser/Thr kinases that regulate various cellular processes, including proliferation, gene expression, and apoptosis. Key mammalian MAPKs include ERK1/2, JNK1-3, p38, and ERK5. [15].

2.2.2 PI3K/AKT/mTOR Pathway

Initiation of signalling through the PI3K/Akt/mTOR pathway occurs through several mechanisms, all of which result in increased activation of the pathway, as commonly seen in many cancer subtypes. Once PI3K signalling is activated, it can act upon a diverse array of substrates including mTOR, a master regulator of protein translation. The PI3K/Akt/ mTOR pathway is an attractive therapeutic target in cancer not only because it is the second most frequently altered pathway after p53. Through its downstream substrates, this pathway controls key cellular processes such as transcription, apoptosis, cell cycle progression, and translation [16].

2.3 The Tumor Microenvironment in PNs

Tumor microenvironments are complex, dynamic systems, varying by tumor type and disease stage. In NF1-associated plexiform neurofibromas, inflammatory mast cells are abundant and appear critical for tumor development. The presence of mast cells in neurofibromas was first documented by Greggio in 1911 and later confirmed in peripheral nerve sheaths and nerve sheath tumors. Histological analyses show significantly higher mast cell numbers in neurofibroma tissue compared to surrounding areas. Vincent Riccardi hypothesized a direct role for mast cells in neurofibroma modulation, though histamine-release inhibitors, while controlling symptoms, did not halt tumor progression [18][19].

3. Current Management Strategies for Inoperable Plexiform Neurofibromas

For large neurofibromas, surgical resection is the primary treatment. However, for inoperable cases, medications are crucial for tumor reduction. Current medications primarily include MEK1/2 inhibitors. While many trials haven't shown significant improvement in progression-free survival (PFS) or partial response (PR) (defined as ≥20% tumor volume decrease), some MEK inhibitors have demonstrated promise. Selumetinib, an MEK inhibitor, achieved PR in 71% and 74% of pediatric patients in Phase 1/2 trials, leading to its FDA approval as the first medical treatment for pediatric plexiform neurofibromas (PN). Similar positive results are being observed in an ongoing Phase 2 trial for adults (NCT02407405). Another MEK inhibitor, binimetinib, in an ongoing Phase 2 study (NCT03231306), shows PR rates of 70% in pediatric and 65% in adult participants with progressive or symptomatic PN. Cabozantinib, a multi-target tyrosine kinase inhibitor, demonstrated a 42% PR rate in a Phase 2 trial for adolescents and adults with inoperable PN (NCT02101736). This trial has also completed enrolment for a pediatric stratum [20].

3.1 Surgical Resection: Limitations and Challenges in Inoperable Cases

Plexiform neurofibromas (PN) can be classified as diffuse or nodular based on imaging. **Diffuse PN** spread widely through connective tissue, engulfing normal structures with ill-defined borders. **Nodular PN** are firm, round, and often appear as multiple discrete tumors originating from peripheral nerves.

Surgical removal of nodular PN, even with careful dissection, carries a high risk of temporary or permanent neurological damage. For diffuse PN, various surgical techniques aim to reduce bleeding and aid excision, such as electrosurgery, using adhesive or thrombogenic substances, or pre-surgical intravascular embolization.

Desmoplastic Nodular Lesions (DNL) are a specific type, characterized by being round, well-demarcated, over 3 cm in their longest diameter, and showing a loss of central core signal, which is typical of classic PN. Nodular PN located superficially to the fascia rarely originate from sensory nerves, but their surgical excision can still lead to sensory paresthesia.

For deep-seated neurofibromas, clinical management involves monitoring disease progression and malignant potential with MRI, and symptom management, which may include surgical excision.[21]

3.2 Conventional Therapies: Chemotherapy and Radiation Therapy

Complete surgical resection is essential for curing Malignant Peripheral Nerve Sheath Tumors (MPNSTs), but local and distant recurrences are common even with aggressive surgery. While radiation and chemotherapy are used, NF1-associated MPNSTs often respond poorly to standard chemotherapy.

The role of radiation therapy (RT) in MPNSTs is evolving. Adjuvant RT is frequently recommended, though only one study has shown a statistically significant increase in local control. RT can achieve local and symptomatic control with tolerable toxicities. Brachytherapy, combined with external beam radiation, has shown promise for local control in soft tissue sarcomas. One study reported an 88% 5-year local control with brachytherapy versus 51% with external beam, while another found external beam superior to brachytherapy for local control.

However, concerns exist regarding RT use in NF1-related plexiform neurofibromas (PN), including an increased risk of RT-induced neoplasms and malignant degeneration of PN into MPNST. There's also a theoretical risk of RT exacerbating pre-existing vasculopathy in NF1 patients. Due to these risks and uncertain benefits, RT is generally avoided for PN, especially in children.[22].

3.3 Symptomatic Management and Other Supportive Care

Initial treatments for plexiform neurofibromas (PNs) with imatinib, tipifarnib, pirfenidone, sirolimus, and interferon alfa-2b offered limited benefit. The major breakthrough came in 2020 with **Selumetinib**, the first effective MEK inhibitor (MEKi) specifically for PN. Selumetinib's side effects in children are generally mild and reversible, including elevated creatine kinase, rash, paronychia, and gastrointestinal issues.

Other relevant drugs include:

- **Cabozantinib:** An oral multikinase inhibitor targeting VEGFR 1/2, MET, and FLT3, approved for various advanced cancers like renal cell carcinoma, medullary thyroid cancer, and hepatocellular carcinoma.
- **Trametinib:** A potent and highly specific MEK1/MEK2 inhibitor, FDA-approved for melanoma, non-small-cell lung cancer, and certain thyroid cancers. An interim analysis of a Phase I/IIa trial showed its promise for medically significant, unresectable PNs in children and adolescents with NF1.
- **Binimetinib:** A potent and selective allosteric inhibitor of MEK1/MEK2, FDA-approved in combination with encorafenib for BRAF-mutant melanoma. Preliminary data indicates it induces partial responses in children with progressive or morbid PNs associated with NF1.[23]

4. Novel Targeted Therapies: Revolutionizing PN Treatment

Advances in understanding plexiform neurofibroma (PN) pathogenesis and the development of realistic preclinical models have paved the way for precision oncology approaches targeting both Schwann cells and the tumor microenvironment. Key improvements in PN clinical trial development include:

1. **3D Volumetric MRI Analysis:** This method offers a more sensitive and reproducible way to measure PN growth and treatment response compared to traditional 1D or 2D analyses, becoming a standard primary endpoint in efficacy trials.
2. **REiNS Collaboration:** This international collaboration has standardized outcome measures for PN clinical trials, accelerating and improving research.[20].

4.1 MEK1/2 Inhibitor-Mirdametinib: A Breakthrough in PN Therapy

Mirdametinib, an investigational oral MEK1/2 inhibitor, was evaluated in the ReNeu trials for its effect on plexiform neurofibromas (PN). The study included 114 subjects (58 adults, 56 children) who received mirdametinib at 2 mg/m2 (max 4 mg) twice daily for 3 weeks on, 1 week off cycles.

Among adults, 41% (24 of 58) achieved a confirmed objective response, significantly exceeding the predefined 23% minimum clinically relevant response rate (P<.001). Of these 24 adult responders, 96% maintained their response, with 75% maintaining it for over 12 months. The median time to confirmed response was 7.8 months. Furthermore, 62% of adult responders experienced a maximum PN volume reduction of over 50% from baseline, with a median time to best response of 15.2 months. Overall, mirdametinib led to deep responses (over 50% PN volume reduction) in 62% of adult responders and 52% of child responders.[24].

4.1.1 Selumetinib: Clinical Trial Evidence and Efficacy

Selumetinib, a highly selective MEK1/2 inhibitor, is FDA-approved for children over 2 with inoperable NF1-associated plexiform neurofibromas. It works by inhibiting the MEK/ERK pathway, which regulates critical cellular responses. Selumetinib's pharmacokinetics are well-understood in both adults and children.Preclinical studies have investigated its brain penetration. Selumetinib is primarily metabolized by Phase I oxidation via cytochrome P450 enzymes (mainly CYP3A4) and by Phase II glucuronidation via UGT1A1 and 1A3. These findings supported its investigation in NF1-related tumors.

In a pediatric Phase 1 trial involving 24 children (median age 10.9) with NF1 and inoperable PN, the maximum tolerated dose (MTD) was determined to be 25 mg/m2/dose twice daily (approximately 60% of the adult recommended Phase 2 dose). All patients exhibited tumor shrinkage (median 31% reduction), and 71% achieved a partial response (PR), with durable PR lasting a median of 23 cycles. These positive results led to the SPRINT study, a Phase 2 trial with 50 children (median age 10.2) receiving the MTD/RP2D of 25 mg/m2/dose twice daily. This trial showed a radiographic PR in 74% of patients, with 28 patients demonstrating durable responses for at least one year and acceptable toxicities.[25].

4.2 Other MEK inhibitors

Cobimetinib-It is a highly selective inhibitor of MEK1/2.Pediatric data for cobimetinib are lacking. Cytotoxic effects have been demonstrated on a number of pediatric cancer cell lines, with activity observed in xenograft models of pediatric solid tumors. Combining cobimetinib and the BRAF inhibitor vemurafenib significantly improved investigator-assessed progression-free survival (PFS) and objective response rate (ORR; both $p < 0.0001$) versus vemurafenib plus placebo in a randomized Phase III study in adults with unresectable/metastatic *BRAF* V600E/K-mutated melanoma which led to the approval of cobimetinib for the treatment of adults in this setting in combination with vemurafenib[26]. ***Binimetinib***-It is an uncompetitive, small molecule inhibitor of selective mitogen-activated protein kinase (*MEK*1/2) which was approved in 2018 in combination with encorafenib for the treatment of metastatic melanomas [27].

5.Conclusion

While both selumetinib and mirdametinib are MEK inhibitors for NF1-associated plexiform neurofibromas (PNs), mirdametinib offers distinct advantages. Mirdametinib, effective in both adults and children per the ReNeu trial, unlike selumetinib's primary pediatric focus, also crosses the blood-brain barrier, making it suitable for associated gliomas. It achieves faster tumor reduction with a better safety profile and fewer adverse effects. Crucially, mirdametinib does not interact with cytochrome P450 enzymes, reducing drug interaction risks. Its availability in both capsule and oral suspension forms also improves administration convenience, especially for children, positioning it as a more versatile and patient-friendly option for symptomatic NF1-PNs.

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