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EVALUATING THE EFFICACY OF TYROSINE KINASE INHIBITORS IN UNRESECTABLE PHEOCHROMOCYTOMA

Abstract: *Pheochromocytoma is a rare neuroendocrine tumor of the adrenal medulla characterized by excessive catecholamine secretion and significant cardiovascular symptoms. While surgical resection is the preferred treatment, a subset of patients presents with unresectable or metastatic disease, for which systemic therapy is required. This study evaluates and compares the therapeutic effectiveness of tyrosine kinase inhibitors and conventional CVD chemotherapy in the management of unresectable pheochromocytomas and paragangliomas.The analysis highlights that tyrosine kinase inhibitors demonstrate better overall tumor control and symptom management, particularly in genetically predisposed cases, while showing a more favorable safety profile. Conventional chemotherapy remains effective for disease stabilization but is associated with a higher burden of treatment-related adverse effects. Overall, the findings support the use of tyrosine kinase inhibitors as a preferred treatment strategy for unresectable pheochromocytomas, especially in patients with resistant disease or specific genetic mutations.*

Key Words: *Unresectable pheochromocytoma, paraganglionomas, CVD therapy, TKIs, disease control rate, progression free survival, partial response.*

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TIROZIN KINAZA INGIBITORLARINI ISHLAMAS FEOKROMOTSITOMADA SAMARADORLIGINI BAHOLASH

Annotatsiya: *Feoxromotsitoma — bu buyrak usti bezi ichki qatlamida rivojlanadigan kam uchraydigan neyroendokrin o‘sma bo‘lib, u ortiqcha katexolaminlar ishlab chiqarilishi va jiddiy yurak-qon tomir simptomlari bilan tavsiflanadi. Jarrohlik usuli asosiy davolash hisoblanadi, ammo bemorlarning bir qismi xirurgik davolab bo‘lmaydigan yoki metastatik shaklda bo‘lib, tizimli terapiyani talab qiladi. Ushbu tadqiqotda xirurgik davolab bo‘lmaydigan feoxromotsitoma va paragangliomalarda tirozin kinaza inhibitorlari va an’anaviy CVD kimyoterapiyasining samaradorligi solishtirilgan. Tahlillar shuni ko‘rsatadiki, tirozin kinaza inhibitorlari genetik moyilligi bo‘lgan bemorlarda o‘smani nazorat qilish va simptomlarni yengillashtirishda yaxshiroq natijalar beradi va xavfsizlik jihatdan ham qulayroq. An’anaviy kimyoterapiya kasallikni barqarorlashtirishda samarali bo‘lsa-da, ko‘proq yon ta’sirlarga olib keladi. Umuman olganda, tadqiqot natijalari tirozin kinaza inhibitorlarini xirurgik davolab bo‘lmaydigan feoxromotsitomalarni davolashda, ayniqsa resistent kasallik yoki ma’lum genetik mutatsiyalarga ega bemorlar uchun afzal strategiya hisoblaydi.*

Kalit so'zlar*: Rezeksiya qilinmaydigan feoxromotsitoma, paragangliomalar, SVD terapiyasi, TKI, kasallikni nazorat qilish darajasi, kasallikning rivojlanishsiz kechish davri, qisman javob.*

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ОЦЕНКА ЭФФЕКТИВНОСТИ ИНГИБИТОРОВ ТИРОЗИНКИНАЗ ПРИ НЕОПЕРАБЕЛЬНОЙ ФЕОХРОМОЦИТОМЕ

Аннотация: *Феохромоцитома — это редкая нейроэндокринная опухоль надпочечников, характеризующаяся избыточной секрецией катехоламинов и выраженными сердечно-сосудистыми симптомами. В то время как хирургическое удаление является предпочтительным методом лечения, часть пациентов имеет неоперабельные или метастатические формы заболевания, требующие системной терапии. В данном исследовании оценивается и сравнивается эффективность тирозинкиназных ингибиторов и традиционной химиотерапии CVD при лечении неоперабельных феохромоцитом и параганглиом. Анализ показывает, что тирозинкиназные ингибиторы обеспечивают лучший контроль опухоли и облегчение симптомов, особенно у пациентов с генетической предрасположенностью, при этом имея более благоприятный профиль безопасности. Традиционная химиотерапия также эффективна для стабилизации заболевания, но сопровождается большим количеством побочных эффектов. В целом, результаты исследования поддерживают использование тирозинкиназных ингибиторов в качестве предпочтительной стратегии лечения нерезектабельных феохромоцитом, особенно у пациентов с устойчивым заболеванием или специфическими генетическими мутациями.*

Ключевые слова: *Неоперабельная феохромоцитома, параганглиономы, ЦВД-терапия, ИТК, степень контроля заболевания, прогрессирование, свободная выживаемость, частичный ответ.*

Relevance: Pheochromocytoma is a tumor that forms in the adrenal gland located above the kidneys, usually located in inner layer known as adrenal medulla. They secretes excessive amounts of catecholamines (primarily Adrenaline and noradrenaline). The occurrence of pheochromocytoma is primarily due to genetic mutation which majorly affects specific molecular signaling pathways inside the adrenal medullary chromaffin cells. The annual incidence of pheochromocytoma globally is approximately 15-20 cases per 10,00,000 people. Equivalent to 1.5-2.0 cases per 100000 people. In case of Uzbekistan the occurrence is equal to global incidence, this is equivalent to a rate of 0.15-0.20 per 10000 people per year. Symptoms of pheochromocytoma majorly includes increased blood pressure, increased heart rate, profused sweating, extreme headache. Other common symptoms list consist of tremors, shortness of breath,anxiety, nausea, weight loss. If patients with pheochromocytomas are not given timely treatment they might develop serious complications such as heart attack, stroke or organ failure. The mutations of pheochromocytoma are classified into 3 main categories. Pseudohypoxia, kinase signaling and wnt altered pathway. 40% cases of pheochromocytoma have an underline germline mutation. The majority of pheochromocytomas when timely initially diagnosed are resectable. Only few percentage of them are non resectable. Approximately 80-85% of the pheochromocytoma are considered resectable (non - metastatic/ localized). Unresectable(metastatic) pheochromocytomas are approximately 10-15 %, they are characterized by the presence of metastasis in sites where chromaffin tissues is not found like bones, lungs, liver, lymph nodes. These makes the pheochromocytomas generally unresectable in advanced stages. Extra adrenal pheochromocytoma also known as paraganglionomas are potentially unresectable and malignant with the rate of metastases upto 25-70% as compared to adrenal pheochromocytomas.

Purpose of Study: To assess the effectiveness and evaluate the therapeutic efficacy of tyrosine kinase inhibitors, investigate the impact of TKIs on tumor response, progression free survival. Also to assess the ability of TKIs to control symptoms related to pheochromocytomas such as hypertension.

Materials and methods: A retrospective cohort study was carried on a total of 116 patients with unresectable pheochromocytomas/ paraganglionomas. Out of the 116 patients 56 (48%) of them were male and 60 (52%) of them were female. Their median age was around 56.3±4.7 years. These 116 patients were divided in two groups on the basis of treatment they were provided. Group 1 consist of 66 patients out of which 29 (44%) were male and 37 (56%) were female and they were administered with sunitinib (50 mg daily). Group 2 to consist of 50 patients out of which 27 (54 %) were male and 23 (46%) of them were female. These patients were administered with CVD (Cyclophosphamide, Vincristine, Dacarbazine) therapy (administered in cycles of 21-28 days) consist of cyclophosphamide, vincristine, dacarbazine. It is a standard chemotherapy therapy regimen which is usually used to control excess catecholamines production and manage symptoms when surgery is not curative. Doses where calculated on the basis of body surface area. Efficacy of both the regimens were compared by taking account into several factors such as disease control rate (DCR), partial response rate (PRR), progression free survival (PFS), Adverse effects of both the regimens. Also SDHB genetic mutation profile was taken into account for the effectiveness of both the regimens, mandatory symptomatic relief and progression free survival were given the utmost importance for analyzing the effectiveness or efficacy of both the regimens during this study.

Results: In group 1 patient which were administered with tyrosine kinase inhibitor (sunitinb) majorly targeted angiogenesisby inhibiting VEGFR which are overly expressed in paraganglionomas. The overall partial response rate was around 40-45%, this rate is increased to 65-70% specifically in patients of SDHB genetic mutation. It showed high disease control rate (DCR) of over 75-88 %. Median progression free survival in this therapy 24-32 months. The overall survival rate is still under monitoring for TKIs and it is to be estimated under 4.8 - 5.3 years. Therapy was more effective in terms of shrinkage of tumor as compared to that of catecholamines level. Strict blood pressure control should be taken into account while initiation of the therapy. 13 patients (20%) under this therapy had shown increased blood pressure which was further managed by alpha blockers. During initiation of the therapy 14 patients (22%) of them had shown hand-foot skin reactions which were resolved further. In group 2 patients which were administered with CVD therapy has shown partial response rate (PPR) of 35-38% a little lower than that of TKIs. As well as the disease control rate (DCR) was around 50% in few patients (5%) it went upto 65% which makes the median value of around 50-55%. The progression free survival shown by patients on traditional CVD therapy was equal to patients on TKIs around 24- 34 months (Figure 1).

Figure 1. Efficacy outcomes in unresectable pheochromocytoma/paraganglioma

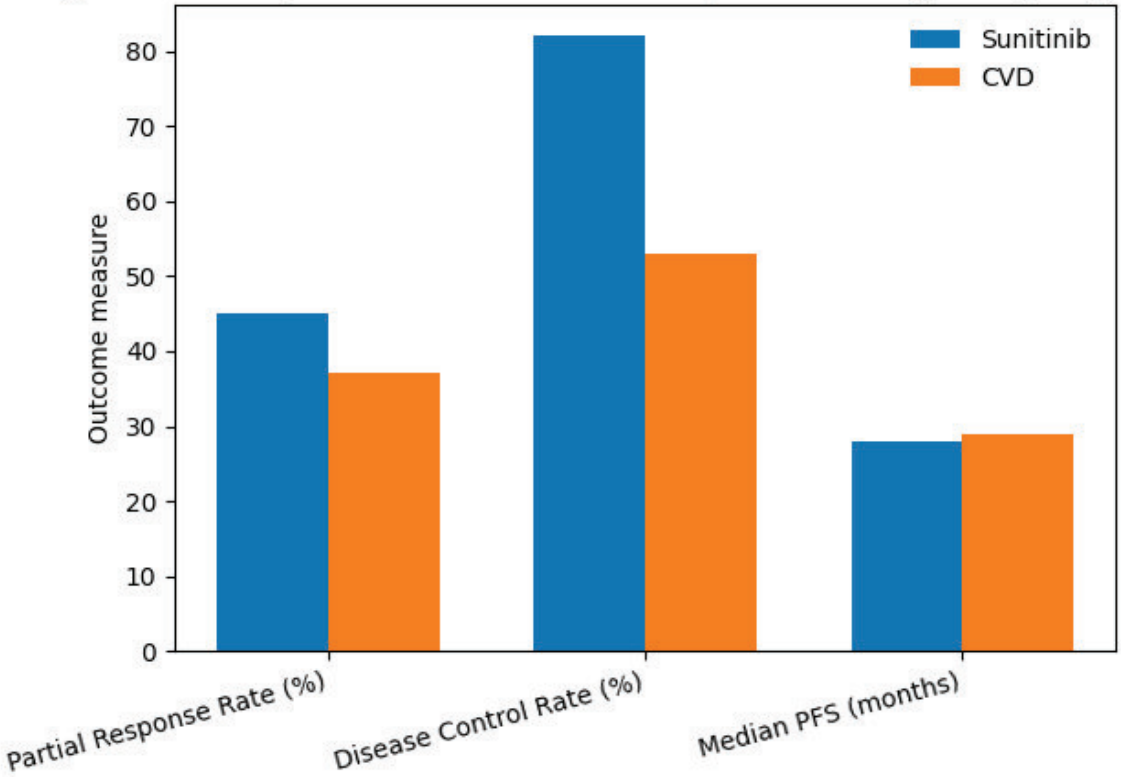


Figure 1. **Efficacy Comparison – Sunitinib vs CVD in patients with unresectable pheochromocytoma**

Sunitinib demonstrates superior tumor control and response rates, while PFS remains similar between the two treatments. This aligns well with the biological rationale of VEGFR inhibition in highly vascular paragangliomas, especially in SDHB-mutated tumors**.**

Side effects component seen in the patients on traditional therapy is 12 patients (24%) had shown myelosuppression (leukopenia, Thrombocytopenia, anemia). 22 (44%) patients had shown gastrointestinal problems (nausea, vomiting, diarrhea) classically seen with alkylating agents. 6 patients (12%) of them shown peripheral neuropathy which is very common with vincristine. As well as common symptoms such as fatigue and Dizziness were seen with majority of the patients.

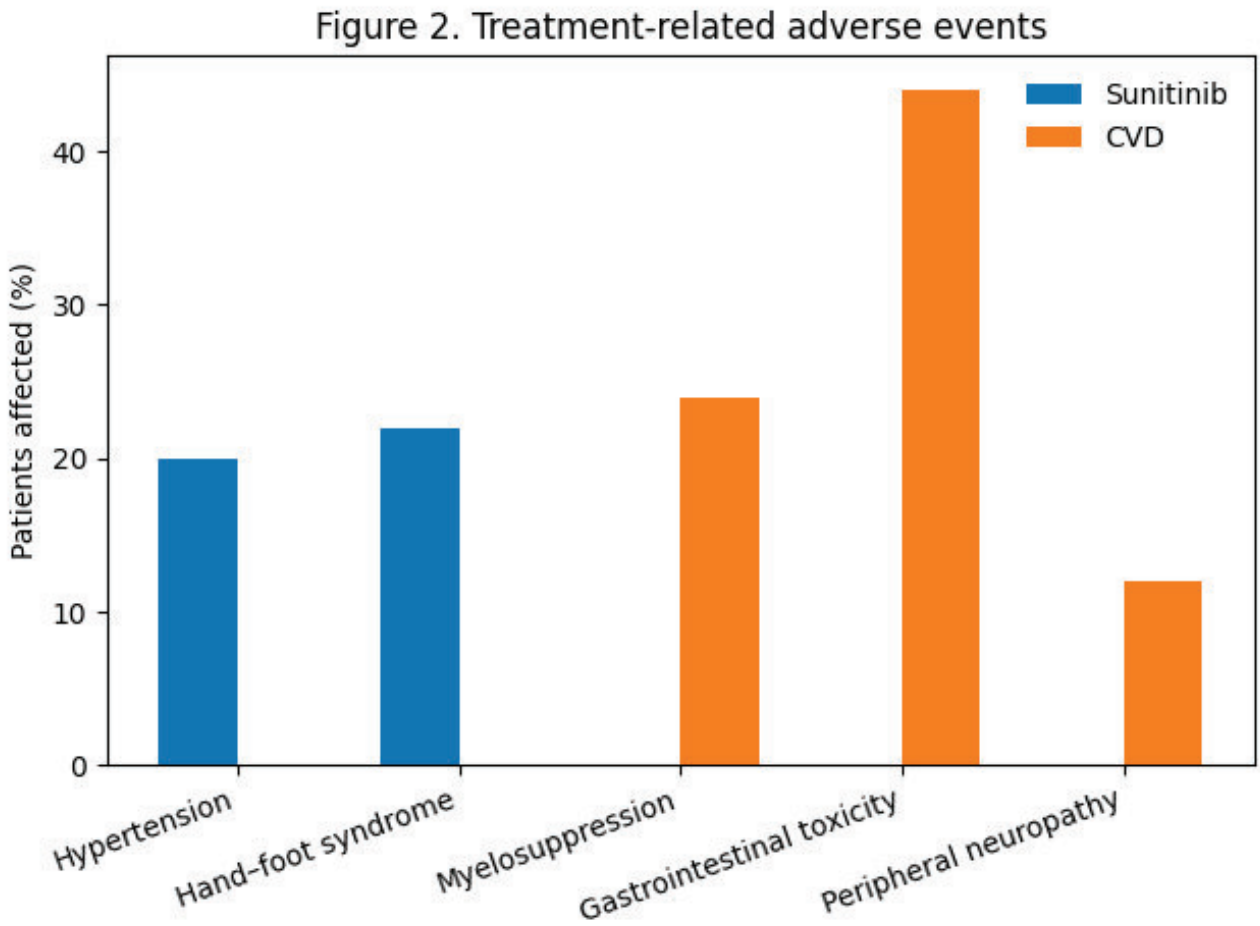


Figure 2. **Treatment-related adverse events associated with sunitinib and CVD therapy**

Sunitinib was primarily associated with hypertension and hand–foot syndrome, whereas CVD therapy showed higher rates of myelosuppression, gastrointestinal toxicity, and peripheral neuropathy.

Conclusion: As a result of the study it can be concluded that for the unresectable pheochromocytomas to reduce the size the best option is tyrosine kinase inhibitors (TKIs). If we compare the study on both the groups, the disease control rate (DCR) was more in group1 as compared to group 2(I.e 75-88%). The overall partial response was slightly on the higher side for patient with TKIs regimen as compared to that of CVD therapy. The median progression free survival was same for both the regimens I.e 24-34 months. Considering the side effects component of both the regimens the patients on CVD therapy had shown more side effects such as myelosuppression, gastrointestinal problems, peripheral neuropathy as compared to that of patients on tyrosine kinase inhibitors. Also tyrosine kinase inhibitors (TKIs) had shown more promising results in case of patients with SDHB genetic mutation with increased disease control rate upto 75-88 %. Considering the resistance to CVD therapy, TKIs had shown promising results for decreasing the size of paragangliomas and for patients with SDHB genetic profile.

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