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Vemurafenib: Pharmacologic Profile, Clinical Applications, and Management in Primary Care and Family Medicine

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Abstract

Background: Mutations within the mitogen-activated protein kinase (MAPK) pathway—particularly BRAF V600 mutations—play a central role in the pathogenesis of malignant melanoma and other malignancies. These mutations drive uncontrolled cellular proliferation and tumor progression. Vemurafenib, a selective BRAF inhibitor, represents a landmark advancement in targeted oncologic therapy.

Aim: This review aims to summarize the pharmacologic profile, clinical indications, safety considerations, and monitoring requirements of vemurafenib, with emphasis on its relevance to primary care and family medicine practice.

Methods: A narrative review was conducted using data from pivotal clinical trials, FDA approvals, and clinical guideline recommendations addressing vemurafenib's efficacy, pharmacokinetics, adverse effects, contraindications, and monitoring strategies.

Results: Vemurafenib demonstrated significant improvements in overall and progression-free survival in patients with BRAF V600E–mutated metastatic melanoma compared with dacarbazine. Common adverse effects include dermatologic toxicity, photosensitivity, QT prolongation, hepatotoxicity, nephrotoxicity, and secondary cutaneous malignancies. Resistance mechanisms frequently develop, supporting the use of combination therapy with MEK inhibitors.

Conclusion: Vemurafenib remains a critical component of precision oncology for BRAF V600–mutant malignancies. Safe and effective use requires careful patient selection, interdisciplinary collaboration, proactive monitoring, and patient education to optimize outcomes and minimize toxicity.

Keywords: Vemurafenib; BRAF V600 mutation; malignant melanoma; targeted therapy; MAPK pathway; primary care oncology.

Introduction

The kinase protein family, comprising MAP, RAS, RAF, MEK, and ERK, plays a critical role in modulating both intracellular and extracellular signaling pathways that govern cellular growth, differentiation, transformation, and programmed cell death. Under normal physiological conditions, these kinases function in a tightly regulated phosphorylation and dephosphorylation cascade, activated by growth factors, to ensure controlled cellular proliferation and tissue homeostasis. Mutations in the genes encoding these kinases disrupt this regulatory cascade, leading to dysregulated cell growth and proliferation, which can contribute to oncogenesis. Among these kinases, the rapidly accelerated fibrosarcoma (RAF) family was initially characterized in 1983 for its role in inducing fibrosarcoma in specific murine models [1]. The RAF family comprises three isoforms—ARAF, BRAF, and CRAF—each encoded by separate, independent genes. BRAF has emerged as particularly significant in clinical oncology, with mutations first reported in approximately 66% of malignant melanomas in 2002. Subsequent investigations revealed BRAF mutations in up to 80% of melanoma cases [2][3]. Beyond melanoma, BRAF mutations have been identified in 40% to 70% of papillary

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thyroid carcinomas and have been implicated in colorectal carcinoma, hepatocellular carcinoma, and virtually all cases of hairy cell leukemia [4][5][6]. These mutations correlate with more aggressive tumor phenotypes and increased mortality, emphasizing their prognostic relevance [7]. The most prevalent activating mutation in BRAF is the substitution of glutamic acid for valine at codon 600, known as the V600E mutation. A less common variant is the V600K mutation, characterized by the replacement of valine with lysine. In contemporary oncology practice, BRAF inhibitors have been developed and approved specifically for the treatment of malignant melanoma harboring BRAF mutations. Notably, these agents have demonstrated limited efficacy in other tumor types possessing BRAF mutations. Vemurafenib was the first BRAF inhibitor approved for clinical use, followed by the development of dabrafenib and encorafenib [8]. These targeted therapies underscore the importance of molecular profiling in guiding precision oncology interventions.

Indications

Vemurafenib has been extensively evaluated through the BRIM clinical trials, including phases I, II, and III, which collectively established its efficacy in patients with malignant melanoma harboring the BRAF V600E mutation. The phase I BRIM trial determined the optimal oral dosing of vemurafenib at 960 mg twice daily, demonstrating acceptable tolerability and a manageable safety profile [9]. Subsequent evaluation in the phase II BRIM trial revealed an overall response rate of 53%, encompassing both partial and complete responses, with a median duration of response of 6.7 months [10]. These findings confirmed the potential of vemurafenib to induce durable tumor regression in patients with advanced melanoma carrying the BRAF V600E mutation. The pivotal phase III BRIM trial, a multicenter randomized controlled study, directly compared vemurafenib with dacarbazine, the then-standard therapy for metastatic melanoma [11]. The trial reported significantly improved overall survival and progression-free survival in the vemurafenib group compared to patients receiving dacarbazine. Although the study faced partial confounding due to crossover from the dacarbazine arm to vemurafenib during interim analysis, subsequent statistical adjustments accounting for crossover still demonstrated a marked therapeutic advantage of vemurafenib. These results were particularly significant in patients with stage IIIC and IV melanoma positive for the BRAF V600E mutation. Based on these outcomes, the United States Food and Drug Administration approved vemurafenib in August 2011. Clinical guidelines, including those from the American Society of Clinical Oncology, recommend the use of vemurafenib in combination with cobimetinib for unresectable or metastatic melanoma harboring a BRAF V600 mutation. Combination immunotherapy with nivolumab and ipilimumab represents an alternative approach in this patient population [12]. FDA-approved indications for vemurafenib encompass metastatic or unresectable melanoma with a confirmed BRAF V600 mutation [13] and Erdheim-Chester disease, a rare non-Langerhans histiocytic disorder [14][15]. Beyond these indications, vemurafenib has been employed off-label in several other malignancies harboring BRAF mutations, including melanoma with a V600K mutation [16], refractory non-small cell lung carcinoma with a BRAF V600 mutation [17], BRAF V600E-positive refractory metastatic or unresectable papillary thyroid cancer [18], and refractory hairy cell leukemia [19][20]. These applications highlight the expanding role of vemurafenib in precision oncology, emphasizing the importance of molecular profiling in selecting patients likely to benefit from targeted BRAF inhibition.

Mechanism of Action

Vemurafenib functions as a potent and highly selective inhibitor of the mutated BRAF V600E kinase, a critical driver in the pathogenesis of several malignancies, most notably melanoma. By binding to the ATP-binding site of the mutated BRAF protein, vemurafenib effectively blocks its kinase activity, thereby disrupting downstream signaling through the mitogen-activated protein kinase (MAPK) pathway. Inhibition of this pathway leads to a reduction in cellular proliferation, induction of apoptosis, and suppression of tumor growth specifically in cells harboring the BRAF V600E mutation. Unlike broader-spectrum kinase inhibitors such as sorafenib, vemurafenib demonstrates minimal activity against wild-type BRAF, enhancing its selectivity and reducing off-target effects [21]. Despite its initial efficacy, disease progression frequently occurs during treatment with vemurafenib due to the emergence of resistance mechanisms within the MAPK pathway. These mechanisms include secondary BRAF mutations, BRAF fusions, or compensatory activation of upstream or parallel pathways, such as alterations in integrins and transforming growth factor beta (TGF-β) signaling [22][23][24]. The clinical recognition of such resistance has led to the development of combination strategies, particularly with MEK inhibitors like trametinib, which target downstream components of the MAPK cascade. Combination therapy has demonstrated improved outcomes in patients with BRAF V600E–positive malignant melanoma, delaying disease progression and enhancing survival compared with monotherapy.

Pharmacokinetic studies have characterized vemurafenib as having a mean oral bioavailability of approximately 64% at steady state, with peak plasma concentrations occurring around three hours after oral administration. Steady-state concentrations are typically achieved within 15 to 22 days. Administration with a high-fat meal substantially

increases drug exposure, with a fivefold increase in area under the curve (AUC) and a 2.5-fold rise in maximum plasma concentration (Cmax), alongside a delayed time to peak (Tmax) of roughly four hours. Vemurafenib exhibits a large apparent volume of distribution of approximately 106 liters and binds extensively to plasma proteins, primarily albumin and α1-acid glycoprotein, with nearly 99% of the drug protein-bound. The drug undergoes hepatic metabolism predominantly via cytochrome P450 enzymes CYP1A2 and CYP3A4, producing metabolites that constitute only about 5% of circulating compounds, with the parent drug representing the remaining 95% [25]. Elimination occurs primarily through fecal excretion, accounting for 94% of the administered dose, with renal excretion contributing approximately 1%. Vemurafenib demonstrates an apparent clearance of 31 L/day and a median elimination half-life of 57 hours, ranging from 30 to 120 hours, supporting a twice-daily dosing regimen in clinical practice.

Administration

Vemurafenib is formulated as an oral tablet, with each tablet containing 240 mg of active drug. This oral route allows for convenient self-administration, but careful attention to dosing schedules is essential to maintain therapeutic plasma concentrations and optimize efficacy. The drug should be administered on an empty stomach or with a low-fat meal, as high-fat meals significantly increase systemic exposure, which may enhance both therapeutic effects and toxicity. Peak plasma levels are typically achieved around three hours post-ingestion, and steady-state concentrations are reached between 15 and 22 days of continuous administration [26]. For adult patients, baseline assessment prior to initiating therapy is crucial. A complete electrocardiogram (ECG) should be obtained to evaluate the QTc interval, as vemurafenib can prolong ventricular repolarization. Therapy should not commence if the QTc exceeds 500 milliseconds due to the increased risk of cardiac arrhythmias. The recommended adult dose is 960 mg administered orally twice daily, with a 12-hour interval between doses. This dosage was determined through the BRIM II trial, which demonstrated both efficacy and tolerability at this level. Treatment should be discontinued in cases of disease progression or the emergence of high-grade toxicity, including severe dermatologic, hepatic, or cardiovascular adverse events [26].

In patients with hepatic impairment, vemurafenib dosing does not require adjustment for mild-to-moderate liver dysfunction. However, caution is advised in severe hepatic impairment due to limited pharmacokinetic data and the potential for hepatotoxicity. Liver function should be closely monitored prior to and during therapy [25]. Similarly, renal impairment does not necessitate dose modification in mild-to-moderate cases, but caution is warranted in severe renal dysfunction. Due to the drug's primarily fecal elimination and minimal renal excretion, the risk of accumulation is low; nonetheless, careful monitoring is recommended in patients with compromised renal function. Pregnancy presents significant considerations for vemurafenib administration. The drug crosses the placenta, and case reports have highlighted severe adverse events, including toxic epidermal necrolysis leading to preterm birth, and neonatal complications such as supraventricular tachycardia requiring intensive care [27][28][29]. These findings underscore the need for stringent risk–benefit assessment prior to use in pregnant individuals. Vemurafenib pharmacokinetics may also be altered during pregnancy, potentially increasing active drug exposure. Consequently, the use of vemurafenib during gestation is generally contraindicated unless potential benefits outweigh risks.

Regarding breastfeeding, clinical data are lacking but given that vemurafenib binds extensively to plasma proteins (>99%), drug transfer into breast milk is presumed to be minimal. However, the long elimination of half-life may result in accumulation in the infant. The manufacturer advises discontinuing breastfeeding during treatment and for at least two weeks after the last dose to avoid potential toxicity [30]. The safety and efficacy of vemurafenib have not been established in pediatric populations, limiting its use to adult patients. In older adults, standard adult dosing is applied, with careful consideration of renal or hepatic function and close monitoring for toxicity. Dose adjustments may be necessary depending on tolerance and the presence of comorbidities. Across all populations, adherence to recommended dosing intervals, regular monitoring of organ function, and early recognition of adverse effects are critical to ensuring both the efficacy and safety of vemurafenib therapy.

Adverse Effects

Vemurafenib is associated with a wide spectrum of adverse effects, predominantly affecting the skin. Cutaneous manifestations are among the most frequently observed, presenting as nonspecific maculopapular eruptions, hyperkeratosis, pruritus, and photosensitivity. Photosensitivity is particularly pronounced when vemurafenib is administered concurrently with radiation therapy, requiring patient education regarding strict photoprotection measures [31]. One of the most clinically significant dermatologic adverse events is the development of secondary skin malignancies. Squamous cell carcinoma (SCC) and keratoacanthoma are observed in up to 30% of patients receiving vemurafenib, with onset typically occurring within weeks of treatment initiation. Less frequently, new primary melanomas may develop, reflecting the complex effects of BRAF inhibition on the mitogen-activated protein kinase (MAPK) signaling pathway. These malignancies are generally managed surgically, often without the need to discontinue vemurafenib therapy [31]. The

paradoxical activation of the MAPK pathway in non-mutant cells underlies the development of secondary melanomas and keratinocyte-derived tumors. Clinical studies have demonstrated that combining BRAF inhibitors with MEK inhibitors, such as cobimetinib, mitigates the risk of cutaneous malignancies. However, this combination therapy is associated with a higher incidence of other dermatologic effects, including rash, dermatitis, and photosensitivity, which require careful monitoring [32].

Beyond cutaneous effects, vemurafenib can induce hepatotoxicity, manifested by elevated liver enzymes, and in rare cases, acute liver injury. Musculoskeletal complaints, particularly arthralgia and myalgia, are also frequently reported. Gastrointestinal disturbances, including diarrhea, nausea, and vomiting, are common and generally manageable with supportive care [33]. Cardiac adverse events, notably QT prolongation, necessitate baseline and periodic electrocardiographic monitoring. In rare instances, vemurafenib has been implicated in the development of Dupuytren's contracture and acute pancreatitis, highlighting the need for vigilance in monitoring for atypical or delayed adverse reactions [34][35]. Vemurafenib is subject to significant drug-drug interactions due to its metabolism and effects on cytochrome P450 enzymes and drug transporters. Strong CYP3A4 inhibitors, such as ketoconazole and clarithromycin, can elevate vemurafenib plasma levels, increasing the risk of toxicity, and should be avoided. Conversely, strong CYP3A4 inducers, including rifampin, phenytoin, and carbamazepine, can reduce plasma concentrations, potentially decreasing drug efficacy. If coadministration with inducers is unavoidable, dosage adjustment may be considered [36]. Vemurafenib also increases the exposure of CYP1A2 substrates, such as tizanidine, necessitating dose reduction or close monitoring during concomitant therapy. Co-administration with ipilimumab is associated with an elevated risk of hepatotoxicity, and this combination should generally be avoided. Additionally, vemurafenib increases the systemic exposure of P-glycoprotein (P-gp) substrates, including digoxin, which may require dose modification or avoidance, particularly for drugs with a narrow therapeutic index [37]. Overall, the adverse effect profile of vemurafenib requires careful patient monitoring and proactive management. Dermatologic surveillance is essential, with regular skin examinations to identify early malignancies or pre-malignant lesions. Periodic laboratory assessments, including hepatic function tests and electrolytes, as well as electrocardiographic monitoring, are recommended to detect systemic toxicity. Clinicians must also review all concurrent medications for potential interactions, adjusting therapy to minimize risk while maintaining therapeutic efficacy. Patient education regarding sun protection, recognition of early symptoms of toxicity, and adherence to monitoring schedules is critical to optimizing the safety and effectiveness of vemurafenib therapy.

Contraindications

Vemurafenib has no absolute contraindications, and its use is generally permitted in all patients who meet the clinical criteria for treatment. The primary limitation to its administration is hypersensitivity to the drug itself, which is rare but may manifest severe allergic reactions. In such cases, the medication should be immediately discontinued, and appropriate supportive measures initiated [38]. This low incidence of absolute contraindications underscores the broad applicability of vemurafenib in patients with confirmed BRAF V600 mutations, particularly in the setting of unresectable or metastatic melanoma.

Warnings and Precautions

One of the major clinical concerns with vemurafenib therapy is the emergence of new primary malignancies. Cases of cutaneous squamous cell carcinoma, keratoacanthoma, and secondary melanomas have been documented, typically developing within the initial weeks to months of treatment. These malignancies arise due to paradoxical activation of the MAPK pathway in BRAF wild-type keratinocytes. Consequently, a comprehensive dermatologic examination should be performed prior to therapy initiation and repeated regularly during treatment. Additionally, patients should be monitored for non-cutaneous malignancies, particularly in individuals with preexisting hematological disorders or other risk factors for RAS-associated tumors [38]. Vemurafenib may promote tumor proliferation in melanoma cells that are BRAF wild-type, as its mechanism of action can paradoxically activate the MAPK signaling pathway in these cells. Therefore, it is essential to confirm the presence of the BRAF V600 mutation in tumor tissue before initiating therapy. Administering vemurafenib in the absence of this mutation may accelerate tumor growth and worsen clinical outcomes. Severe dermatologic reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug reaction with eosinophilia and systemic symptoms (DRESS), have been reported. Should any of these life-threatening reactions occur, immediate cessation of vemurafenib is mandatory [39][40]. Photosensitivity reactions are also common, ranging from mild erythema to severe sunburn. Patients must employ strict photoprotection measures, including high-SPF sunscreen, protective clothing, and avoidance of direct sunlight. In cases of intolerable photosensitivity, dosage modification may be necessary.

Cardiac toxicity is another critical consideration. Vemurafenib can prolong the QT interval, posing a risk for serious arrhythmias. Baseline and periodic ECG monitoring are essential. The drug should be withheld if the QTc interval

exceeds 500 milliseconds. Therapy may resume at a reduced dose once the interval normalizes, but persistent prolongation despite correction of modifiable risk factors necessitates permanent discontinuation. Ophthalmologic complications, such as uveitis and blurred vision, have been observed during treatment. These adverse effects necessitate prompt evaluation by an ophthalmologist to prevent long-term visual impairment [41]. Embryo-fetal toxicity is a further concern; vemurafenib crosses the placenta and may cause developmental harm. Women of reproductive potential must employ effective contraception throughout therapy and for at least two weeks after the final dose. Patients receiving radiation therapy concurrently or sequentially should be monitored carefully for radiation sensitization and recall reactions, which may exacerbate tissue damage [42]. Renal toxicity, including acute interstitial nephritis and acute tubular necrosis, has also been reported. Regular monitoring of serum creatinine and renal function is crucial, as vemurafenib-induced mitochondrial dysfunction may contribute to nephrotoxicity [43][44]. In summary, vemurafenib requires careful patient selection and monitoring due to risks of secondary malignancies, dermatologic toxicity, QT prolongation, ocular effects, embryofetal toxicity, radiation interactions, and renal injury. These precautions are essential to maximize therapeutic benefit while minimizing potentially life-threatening adverse events.

Monitoring

Patients receiving vemurafenib require meticulous clinical monitoring to ensure both efficacy and safety during therapy. Dermatologic surveillance is particularly important, as the drug is associated with a high incidence of cutaneous adverse effects, including the development of secondary malignancies such as squamous cell carcinoma, keratoacanthoma, and melanoma. Skin examinations should be performed at baseline and continued periodically throughout treatment. Early identification of suspicious lesions allows for prompt intervention, typically through surgical excision, without necessarily interrupting vemurafenib therapy [45]. In addition to dermatologic monitoring, the American Society of Clinical Oncology recommends that all cancer patients be screened for hepatitis B virus (HBV) infection prior to initiating systemic therapy. This screening includes assessment of hepatitis B surface antigen (HBsAg), hepatitis B core antibody, and hepatitis B surface antibody. Patients with evidence of chronic HBV infection should begin antiviral therapy concurrent with cancer treatment and continue for a minimum of 12 months after therapy completion to prevent viral reactivation [45]. HBV DNA levels should be measured at baseline and every six months during treatment. Following cessation of antiviral therapy, HBV DNA should be monitored monthly for the first three months, then quarterly thereafter. For patients at high risk of reactivation, continued monitoring and therapy are crucial, while those receiving low-risk regimens require monitoring primarily of HBsAg. Post-therapy monitoring is generally unnecessary unless clinical or laboratory findings suggest viral reactivation. Laboratory assessments are also a key component of patient monitoring during vemurafenib therapy. Liver function tests should be obtained at baseline and repeated at regular intervals to detect potential hepatotoxicity early. Similarly, renal function should be evaluated before initiating therapy and periodically throughout treatment to identify nephrotoxic effects. Electrocardiograms (ECGs) are recommended at baseline and at scheduled intervals to detect QT interval prolongation, which can predispose patients to serious cardiac arrhythmias. By implementing structured monitoring protocols across dermatologic, hepatic, renal, and cardiac domains, clinicians can optimize patient safety while maintaining the therapeutic benefits of vemurafenib [45].

Toxicity

Vemurafenib is associated with multiple organ-specific toxicities, which require vigilant monitoring and timely intervention to prevent severe complications. Cutaneous toxicity is among the most frequently observed adverse effects, including phototoxic reactions, rash, hyperkeratosis, and the development of secondary skin malignancies such as squamous cell carcinoma or keratoacanthoma. Phototoxicity often presents as exaggerated sunburn reactions in exposed areas, necessitating patient education on strict sun protection measures, including broad-spectrum sunscreen application and protective clothing. Ocular toxicity, including uveitis and blurred vision, has also been reported, highlighting the importance of slit-lamp examination and ophthalmologic evaluation at baseline and during therapy [46]. Renal toxicity is another significant concern. Vemurafenib can induce acute interstitial nephritis and tubular necrosis, which may present as rising serum creatinine, oliguria, or electrolyte disturbances. Regular monitoring of renal function, including serum creatinine and estimated glomerular filtration rate, is essential to detect early renal impairment and prevent progression to severe kidney injury. Hepatic toxicity is less common but can manifest as elevated liver enzymes, necessitating periodic liver function testing. Cardiotoxicity, particularly QT interval prolongation, is clinically significant and can predispose patients to arrhythmias. ECG monitoring is recommended at baseline and at regular intervals, with immediate intervention if QTc exceeds safety thresholds. Management of vemurafenib toxicity involves dosage adjustments tailored to severity. For initial toxic reactions, the dose may be reduced from the standard 960 mg twice daily to 720 mg twice daily. In cases of recurrent or high-grade toxicity, further reduction to 480 mg twice daily may be warranted. Doses below this threshold are considered subtherapeutic and may compromise

treatment efficacy. Temporary treatment interruption may also be required in severe toxicity, followed by gradual dose reintroduction once the patient stabilizes. Supportive care measures, such as topical therapies for skin reactions or hydration for renal protection, are integral to comprehensive toxicity management. Close clinical monitoring and patient education are essential to maximize therapeutic benefit while minimizing adverse effects [45][46].

Enhancing Healthcare Team Outcomes

The use of vemurafenib in the management of advanced malignant melanoma underscores the importance of a coordinated, interprofessional healthcare team to optimize patient outcomes. As the first BRAF inhibitor approved for this indication, vemurafenib has demonstrated improvements in overall survival, yet its clinical use is complicated by significant adverse effects and the need for intensive monitoring. The financial burden of the medication and the potential for serious toxicities, including cutaneous malignancies, hepatotoxicity, nephrotoxicity, and cardiotoxicity, further necessitate close collaboration among healthcare professionals to ensure safe and effective therapy. Oncologists are primarily responsible for establishing the treatment plan, determining eligibility based on BRAF V600 mutation status, and overseeing the patient's overall clinical trajectory. Primary Care Physicians (PCPs) and Advanced Practice Providers (APPs) contribute by monitoring signs of toxicity, managing comorbid conditions, and facilitating timely interventions. Their ongoing assessment of renal and hepatic function allows for dose adjustments and early detection of complications, ensuring continuity of care across outpatient and inpatient settings. Pharmacists play a critical role in optimizing drug therapy, assessing potential drug-drug interactions, and advising the care team on appropriate dose modifications. They also educate patients about adherence, drug storage, and management of side effects. Oncology nurses serve as frontline patient educators, emphasizing the importance of self-monitoring for skin changes, sun protection, and reporting of symptoms such as visual disturbances or unexplained fatigue. They provide direct patient support during treatment administration and coordinate care with other team members. The integration of these disciplines fosters a collaborative environment in which adverse reactions are identified early, patient education is reinforced, and therapeutic efficacy is maximized. An interprofessional approach ensures that the complex needs of patients receiving vemurafenib are addressed comprehensively, reducing morbidity and enhancing quality of life. This model of care highlights the necessity of structured communication, shared decision-making, and continuous monitoring in achieving favorable clinical outcomes for patients undergoing targeted cancer therapy [45][46].

Conclusion:

Vemurafenib represents a major therapeutic advance in the management of malignant melanoma and other rare BRAF V600–mutated malignancies by directly targeting a key oncogenic driver within the MAPK signaling pathway. Clinical trials have consistently demonstrated its ability to improve survival outcomes and induce meaningful tumor regression in appropriately selected patients. However, its benefits are tempered by the development of resistance and a complex adverse-effect profile that necessitates vigilant clinical oversight. From a primary care and family medicine perspective, clinicians play a vital role in the early identification of treatment-related toxicities, coordination of interdisciplinary care, and long-term patient monitoring. Dermatologic surveillance is particularly crucial due to the high incidence of secondary skin malignancies, while routine cardiac, hepatic, renal, and ophthalmologic assessments are essential to mitigate potentially life-threatening complications.

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