Indian Journal of Biochemistry & Biophysics
Vol. 63, July 2026, pp. 739-760
DOI: 10.56042/ijbb.v63i7.26605

A Review

Vincristine in haematological malignancies: A cornerstone alkaloid in modern cancer chemotherapy

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Received 16 December 2025; revised 09 May 2026

Vincristine sulfate, a naturally occurring vinca alkaloid from *Catharanthus roseus*, remains a crucial component of polychemotherapeutic regimens for a wide range of haematological malignancies, including acute lymphoblastic leukemia (ALL), Hodgkin's lymphoma, and non-Hodgkin's lymphomas. Vinca alkaloid relies on its antineoplastic property to interfere with the microtubule's dynamics, thereby, it stops mitosis, inducing apoptotic cascades in rapidly dividing cells. Vincristine is being utilised in chemotherapy formulation due to its high-affinity binding to tubulin dimers, which inhibits microtubule assembly and induces mitotic arrest and apoptosis during the mitotic M-phase of the cell cycle. Since lymphoid and myeloid neoplasms proliferate quickly, vincristine offers a targeted cytotoxic advantage with a distinct, bone-marrow-sparing toxicity profile. As vincristine does not significantly impair myelosuppression, it can be incorporated into dose-intensive, multi-drug regimens that have greatly increased survival rates in both adult and paediatric populations. However, its clinical utility is often challenged by dose-limiting peripheral neurotoxicity and emerging resistance mechanisms. There is a substantial gap in standardised vincristine toxicity assessment, pharmacogenomic prediction, and targeted drug delivery systems, highlighting the need for continued investigation. This review investigates current pharmacological aspects and clinical outcomes, vincristine's status as a therapeutic agent in curative-intent regimens while evaluating recent innovations, like liposomal formulation and structural modifications, designed to enhance delivery and mitigate adverse effects like toxicity and other oncologic factors, including its clinical uses and limitations.

Keywords: Acute lymphoblastic lymphoma (ALL), Drug resistance, Liposomal formulation, Microtubule inhibition, Neurotoxicity

Introduction

Vincristine, one of the alkaloids, monoterpenoid indoles derived from Madagascar periwinkle (*Catharanthus roseus*), has been a standard chemo-therapeutic agent for haematological malignancies for more than sixty years. Acting through interference with microtubule dynamics, where the drug binds to the β-subunit of tubulin dimers and subsequently blocks microtubule polymerization, it has arrested the process of disease among so many patients. The arrest of dividing cells in the metaphase and commencement of intrinsic apoptotic pathways make it an all-too-potent weapon against rapidly dividing malignant cells[1]. Vincristine was first introduced into practice in the early 1960s and quickly became a keystone of multidrug therapy for haematologic malignancies like acute lymphoblastic leukaemia (ALL), Hodgkin lymphoma, non-Hodgkin lymphoma, Burkitt lymphoma, among others. Its introduction

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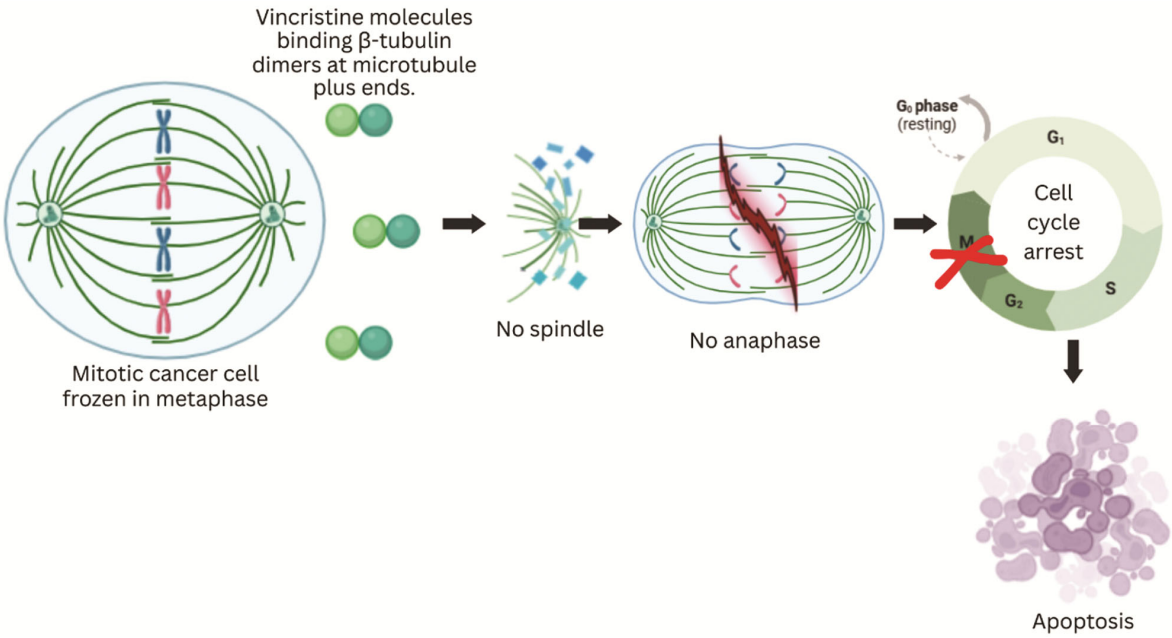

Graphical abstract

transformed how paediatric oncology was conducted, increasing survival from nine percent to 90 percent in childhood ALL[2].

The treatment benefits of vincristine are thus its phase-specific cytotoxicity, mostly killing mitotic cells with a much less crippling myelosuppressive effect than alkylating agents or anthracyclines. Due to its synergistic activity and ability to induce deep remissions in all lymphoid malignancies, it also remains part of standard combination chemotherapy regimens such as CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) and Hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone), as well as in children's regimens such as VCR/ASP/dexamethasone[3]. Despite this importance, the therapeutic ability of vincristine is compromised by a narrow safety margin, predominantly because of its dose-limited neurotoxicity. Vincristine-induced peripheral neuropathy (VIPN) occurs owing to strikingly serious disturbances in axonal microtubules, which are critical for the transport of vesicles and mitochondria within the neurone. The neurotoxic action is generally cumulative and irreversible, especially in children or patients with genetically polymorphic activity related to CYP3A5-mediated metabolism[4].

These attempts to increase the therapeutic index of vincristine have led to extensive pharmaceutical research. All of these liposomal encapsulation technologies include the vincristine sulphate liposome injection (brand name Marqibo), which was also designed with the objective of ameliorating vincristine pharmacokinetics by prolonged circulation time, increasing tumour deposition, and lowering off-target exposure to peripheral nerves. Approval was received for acutely relapsed or refractory Philadelphia chromosome-negative ALL, but gains haven't been made because of mixed clinical trial outcomes and exorbitant costs of these products[5]. Biodegradable polymeric nanoparticles have evolved thus far among the more advanced platforms of drug delivery; antibody-drug conjugates and increasingly sophisticated devices such as pH-sensitive liposomes have also conquered multidrug resistance and made possible the target-specific cytotoxicity of tumour cells with low collateral damage[6].

Along with reformulations, combination regimens involving vincristine and promising immunotherapies and small molecule inhibitors are being evaluated to maximize the joint benefits of synergy. Convergence between vincristine cytostatic activity and immune checkpoint blockers, as well as CD20-targeted antibodies (such as rituximab), offers substantial opportunities to create combination treatment regimens with reduced adverse effects without compromising or even enhancing antitumour activity[7]. In addition, the pharmacogenomic approach is increasingly trending, wherein genomic profiling now allows stratifying patients based on either their

susceptibility to neurotoxicity or their likelihood of a therapeutic outcome. New advances have identified the SNPs at the promoters of CEP72 and ABCB1 polymorphisms as biomarkers for the risk of VIPN and altered clearance of vincristine[8].

While haematologic oncology is starting to offer precise therapy, in the definition of vincristine, the drug is considered not only a cytotoxic agent but also a potential candidate for optimisation by formulation science, dosing according to biomarkers, and rational combinations. However, while traditional regimens already legitimated its relevance, current research shrank the toxicity footprint while elevating the selectivity and breadth of application to resistant or refractory disease. This review reframes the mechanistic upfront basis of vincristine, clinical usage, toxicity profile, mechanisms of resistance, and recent pharmaceutical achievements, concentrating specifically on changes relating to the five years that could recast its function as a contemporary oncological practice (Table 1).

Mechanism of Action

Vincristine is an extremely potent antineoplastic compound, and its cytotoxic action is primarily due to its disruption of microtubule dynamics necessary for cell division. Its action on beta-tubulin inhibits the polymerisation of microtubules from tubulin dimers that are important for the assembly of the mitotic spindle during cell division. This inhibition of microtubule formation by vincristine will effectively inhibit the assembly into a functional mitotic spindle, thus causing metaphase arrest. Breaking this spindle effectively poisons mitosis, blocking the separation of the chromosomes and their exit from the cell cycle[9]. So, it interferes with the segregation of chromosomes and cytoplasmic division that causes cellular stress and cell death.

Microtubule Targeting and Disruption of the Spindle Apparatus

Unlike taxanes, vincristine binds to a second site on β-tubulin and acts at nanomolar concentrations to prevent microtubule polymerisation. Vincristine thereby destabilises microtubules and inhibits spindle assembly during mitosis, especially in haematologic malignancies characterised by a high proliferation index, activating the spindle assembly checkpoint (SAC). When this happens, SAC keeps the cell cycle from moving from metaphase to anaphase and stops chromosomes from segregating. Cells continue to be held in mitosis, which can lead to a mitotic catastrophe, a kind of cell death resulting from the activation of pro-apoptotic pathways and DNA fragmentation.

It is thus not simply a holding of the cell cycle at the metaphase; it sets off cascades of molecular disturbances: perturbations of mitochondrial function, endoplasmic-reticulum stress, and crippling survival signalling networks like PI3K/Akt and MAPK. Eventually, these disturbances lead to the programmed-death course in all cells, but in cells like leukaemic and lymphoma cells, which are very fast-dividing and have fewer repair mechanisms, the process becomes more accelerated[10].

Induction of Apoptosis

Thus, vincristine-triggered mitotic arrest leads to a whole battery of intracellular stress messages, finally funnelling to programmed cell death. The intrinsic (mitochondrial) mechanism of apoptosis would be the first to be activated. Prolonged SAC activation results in cumulative pro-apoptotic signals like BIM, PUMA, and NOXA, which in turn lead to mitochondrial outer membrane permeabilisation (MOMP). This MOMP will unleash cytochrome c into the cytosol, which will bind Apaf-1 and procaspase-9 to produce an apoptosome for activating the caspase cascade. Casually, executioner caspases, particularly caspases

Table 1 — Comparison of Traditional and Biotechnological Vincristine Production Methods

Aspect	Traditional Plant-Based Production	Plant Cell Culture/ Fermentation	Synthetic Production
Source	*Catharanthus roseus* plant	Plant cells or genetically engineered microorganisms	Synthetic chemical synthesis
Yield	Low, labor-intensive	Higher yields, scalable	Potentially high but not yet cost-effective
Production Time	Long (several months)	Moderate (weeks to months)	Long and complex (multi-step process)
Cost	High (due to agricultural inputs and extraction methods) [12]	Moderate (bioreactor cost, fermentation medium)	Very high (due to synthesis complexity)
Environmental Impact	Significant (agricultural land use, pesticide use)	Reduced (bioreactors, less land use)	High (energy-intensive processes)

3 and 7, undergo activation to initiate a network followed by degradation of cytoskeletal proteins and DNA repair enzymes alongside nuclear lamins, leading to aspects such as shrinkage of the cell, membrane blebbing, and fragmentation of DNA. Aligned with this, the general scenario in vincristine-treated haematologic malignancies is downregulation of anti-apoptotic proteins such as Bcl-2 and Bcl-xL, further tipping the balance toward apoptosis[12].

Models all show vincristine also evokes caspase-independent cell death in half-intact p53 cells or apoptosis-resistant cells. In such cases, the mitochondria are compromised to give rise to the nuclear movement of apoptosis-inducing factor (AIF) and endonuclease G to facilitate chromatin condensation and caspase-independent fragmentation of DNA[6]. This binomial capacity of inducing caspase-dependent and -independent forms of apoptosis gives vincristine a successful pathway in chemoresistant leukaemia and lymphomas. Because of the heavy dependence of vincristine cytotoxicity on target cell proliferation, haematologic malignancies like ALL, Burkitt lymphoma, and high-grade non-Hodgkin lymphomas make very viable targets for mitotic arrest and apoptosis by vincristine, since they contain proliferating lymphoid progenitors. The absence of mature cell cycle checkpoints and pronounced dependence on microtubule dynamics provide such entities for selective targeting[13].

However, it affects not only neoplastic cells but also other tissues like intestinal crypts, bone marrow progenitors, and follicular keratinocytes, resulting in side effects like mucositis, myelosuppression, and alopecia, respectively. Although myelosuppression effects due to vincristine are comparatively mild compared to other agents, their consideration during intensive treatment regimens involving combinations with other myelosuppressive agents is still clinically imperative. The most prominent non-target toxicity to occur involves vincristine-induced peripheral neuropathy (VIPN). Neurones, especially those with long peripheral axons, are highly vulnerable to microtubule disruption owing to the transport of goods along axons requiring intact microtubules. Disruption of kinesin- and dynein-driven transport of vesicles, mitochondria, and neurotransmitter granules by vincristine will result in degeneration of axons and develop clinical symptoms of neuropathy, including paraesthesia, muscle weakness, and gait disturbance[14]. Through pharmacogenomic studies, it has been established that patients with polymorphisms in the *CEP72* promoter, reduced *CYP3A5* activity, or altered expression of ABCB1 are at an evidently higher risk for developing severe neuropathy or toxic accumulation of plasma drug. Thus, pharmacognosy-guided vincristine dosing is the most welcome and emerging practice, especially in paediatric and adolescent oncology settings.

Resistance Mechanisms

Vincristine has managed to accomplish a lot in the treatment of haematopoietic malignancies; however, the eventual appearance of resistance to vincristine has limited its long-term therapeutic applications. The vincristine resistance is intrinsic or acquired due to some very complex interaction of pharmacokinetic barriers, overexpression of efflux transporters, a shift in microtubule structure, and deficiencies in the cell death signalling pathway.

Among the mechanisms of resistance, the most well-characterised and well-studied is the overexpression of ATP-binding cassette (ABC) transporters, whose most relevant member in vincristine resistance is P-glycoprotein (P-gp) coded by the *ABCB1* gene (also known as MDR1). It basically activates the P-glycoprotein (P-gp)-dependent ATP efflux pump, which excretes the toxic vincristine associated with many other vinca alkaloids out of malignant cells, thereby reducing their intracellular therapeutic drug concentrations below therapeutic drug amounts. After engaging in numerous exposures to chemotherapeutic agents, this has typically been amplified and is characteristically associated with multi-drug resistance (MDR) in leukaemia and lymphomas[15].

β-tubulin isotype mutations, especially βIII-tubulin overexpression (TUBB3), have been associated with reduced binding of vincristine an efflux-based mechanism. It is different from the other isotypes structurally having unique structural plasticity and resistance to being destroyed by destabilization-induced changes in conformation by microtubule-destabilizing agents. Increased TUBB3 expression is common among vincristine-resistant subclones of lymphoid cancers and is associated with poor treatment responses to spindle poisons[16].

Another important mechanism of resistance involves defective apoptotic signalling. Cell killing may be avoided by cancer cells, even in the presence of an effective mitotic arrest, by compromised apoptotic execution downstream from that arrest.

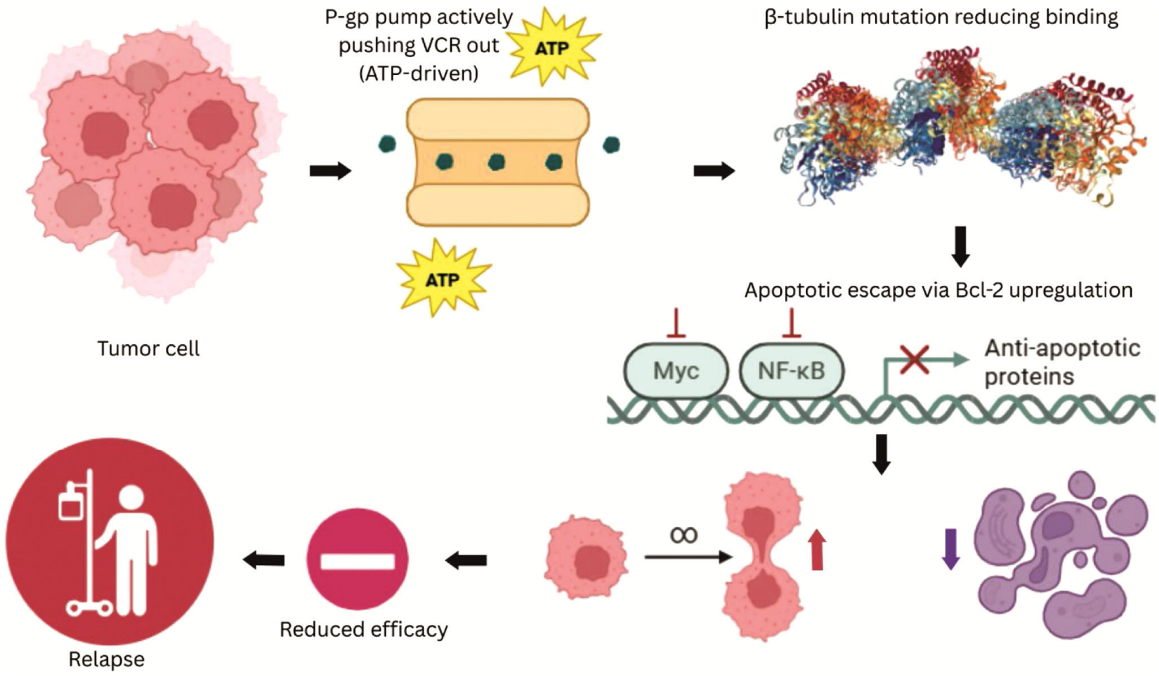

Fig. 1 — Cancer cells develop resistance to vincristine through multiple mechanisms including overexpression of P-glycoprotein, mutations in β-tubulin isoforms, and evasion of apoptosis *via* anti-apoptotic signalling pathways

Anti-apoptotic Bcl-2 family proteins overexpressed (Bcl-2, Bcl-xL, Mcl-1) or mutation of caspase genes would inhibit the intrinsic death pathway activated by vincristine. Some tumours show a lower response to vincristine indeed because of TP53 mutations controlling pro-apoptotic transcriptional programs in response to damage caused by the mitotic process. Changes in epigenetics have also been noted. Pro-apoptotic genes are switched off because of hypermethylation of DNA or deacetylation of histones at their promoter elements such as BAX or PUMA, which thus prevent survival under vincristine stress. It is now becoming increasingly evident from fresh discoveries that chromatin remodelling and noncoding RNAs such as miRNAs play roles in resistance directed against drug-metabolizing enzymes and regulators of tubulin[17] (Fig. 1).

Ultimately, cells manage to escape from mitotic arrest through mitotic slippage, which involves either the way that the cell passes mitosis altogether-or in having disturbed the SAC in the first stage-or divides the cell but avoids the mitosis itself. However, these pseudo-G1 cells may reactivate their cell cycle after that, undergo differentiation, or enter a senescence-like state, further reducing their susceptibility to being damaged by mitosis-specific cytotoxins, such as vincristine[18]. Current efforts to circumvent resistance include concurrent administration of P-gp inhibitors along with vincristine or possibly nanoparticle-based formulations of vincristine that circumvent efflux pumps as well as combinations with apoptosis sensitizers, epigenetic modulators, or immune checkpoint inhibitors to evade survival benefit-resistant clones.

Non-Mitotic Effects of Vincristine

While the canonical mechanism of vincristine predominantly acts on mitosis, increasing interest is being paid to its non-mitotic (interphase) effects which contribute distinctly to its cytotoxic profile and, paradoxically, the dose-limiting toxicity especially in terms of neuropathy. Microtubules in non-dividing cells are important for maintaining the shape of cells, intracellular trafficking, and involved in signal transduction. Interphase cells, especially neurons, endothelial cells, and immune cells, further interfere in the above functions by changing the cytoskeletal network destabilized by vincristine in actions leading to cell dysfunction causing a wider extent of cellular functional impairment.

In the axon, vincristine obstructs more long axonal transport of mitochondria, synaptic vesicles and neurotrophic signals by inhibition of kinesin and dynein motor proteins that move along microtubule tracks. Blockade at this point renders distal axon

terminals deprived of energetic support, generates localized oxidative stress, disturbs calcium homeostasis, and eventually degenerates the axon. These mechanisms create the basis of vincristine peripheral neuropathy (VIPN), with greater severity in children and in patients with inherited or acquired transport defects[19].

It also goes beyond nerves then into endocytosis and the trafficking of receptors, for example. It has been shown that vincristine prevents internalization and recycling of important reagents of signalling, including the EGFR, CXCR4, and integrins, and thereby reduces cellular responsiveness to the environment. This interference in the aforementioned cellular activities occurs in tumour cell adhesion, migration, and invasion, which hints at the possibility of vincristine-endorsed anti-metastatic effects without using the arrest activity during mitosis[20].

Thus, vincristine also disrupts various signalling pathways by failing to locate kinases and second messengers properly. For example, destruction of microtubule-based trafficking inhibits localisation of Akt to the plasma membrane, preventing PI3K/Akt signalling. Downregulation of mTOR activity and inhibition of translation and growth-related gene expression are results of this. Similarly, upstream perturbations observed with mitogen stimulation were noted for MAPK/ERK signalling and those that follow activation from cytokines using the JAK/STAT pathway owing to exposure to vincristine, especially in resistant leukaemia cells[11].

Interestingly, vincristine also sensitises tumours to immunotherapy through its non-mitotic actions. It also disrupts vesicular transport and surface presentation of immune checkpoint proteins such as PD-L1, thus augmenting T-cell-mediated cytotoxicity in lymphoma models. These findings open new avenues of research to assess vincristine's value as an immunomodulatory co-agent in haematologic oncology[21].

Clinical Applications

Vincristine has remained one of the mainstays of chemotherapeutic treatment for patients with haematological malignancies and childhood cancer. Its use in combination with other agents in chemotherapeutic regimens has resulted in significant improvements in the incidence of long-term remission and survival, especially for diseases with a high mitotic index, such as acute lymphoblastic leukaemia, Hodgkin lymphoma, and non-Hodgkin lymphoma (Table 2). Further updates on its dose optimisation as well as form and combination with immunotherapies have widened the range of verity it applied to first-line and relapse scenarios[22].

Acute Lymphoblastic Leukaemia (ALL)

Vincristine is one of the principal drugs in therapy for paediatric and adult acute lymphoblastic leukaemia (ALL). It is usually used in induction and consolidation phases in virtually all frontline regimens, including BFM (Berlin–Frankfurt–Münster), St. Jude Total Therapy, and COG regimens. Its high activity against rapidly growing lymphoblasts, coupled with a low myelosuppressive toxicity profile, makes it suitable for prolonged dosing together with glucocorticoids, anthracyclines, and asparaginase[23].

The vincristine-containing regimens played a very substantial role in the attainment of more than 90% in complete remission and of long-term event-free survival over 85% in standard-risk patients in the treatment of paediatric ALL. Current studies on the prevention of vincristine-induced peripheral neuropathy (VIPN) now involve pharmacogenomic stratification, particularly among *CEP72* or *CYP3A5* polymorphism carriers, without compromising efficacy through precision-guided dose adjustment (Fig. 2).

In adults, high-risk or Philadelphia chromosome-negative positive B-ALL is still treated with curative-intent and palliative-vincristine-inclusive regimens. More importantly, vincristine sulphate liposome

Table 2 — Common Clinical Applications of Vincristine in Haematological Malignancies

Cancer Type	Indication[29]	Treatment Regimen	Vincristine Dosage
Acute Lymphoblastic Leukaemia (ALL)	First-line treatment in paediatric and adult ALL	Part of multi-agent chemotherapy regimens (*e.g.*, VCR, L-asparaginase)	1.5–2 mg/m², weekly
Hodgkin Lymphoma	Part of chemotherapy in combination regimens	ABVD regimen (Adriamycin, Bleomycin, Vincristine, Dacarbazine)	1.4–2 mg/m², every 2-4 weeks
Non-Hodgkin Lymphoma	Part of chemotherapy for advanced stages	CHOP regimen (Cyclophosphamide, Doxorubicin, Vincristine, Prednisone)	1.4–2 mg/m², every 3 weeks
Neuroblastoma	Used in high-risk cases or relapsed disease	Part of high-dose chemotherapy regimens for neuroblastoma	1.4–2 mg/m², weekly

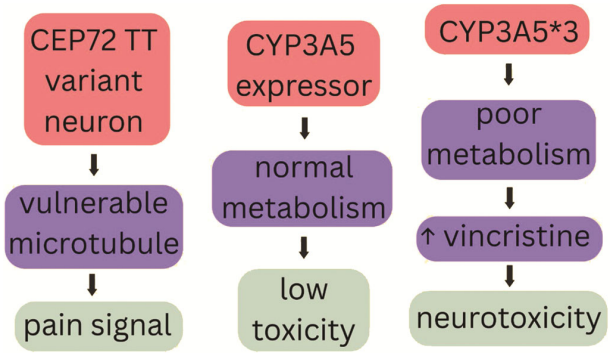

Fig. 2 — Polymorphisms affecting *CYP3A5* and *CEP72* genes are involved in vincristine pharmacokinetics and development of neuronal sensitivity including peripheral neuropathy. Higher vincristine concentration lowers the *CYP3A5* expression, connecting to neurotoxic effects. Reduction in the expression of *CEP72* gene in human acute lymphoblastic leukemia cells increase their sensitivity to vincristine

injection (VSLI; Marqibo®) is greatly successful in relapsed/refectory cases of ALL because of its long half-life time and the high tumour exposure[29]. While availability and expense may continue to be barriers, VSLI is arguably an important development within the whole scheme of vincristine pharmacology.

Hodgkin and Non-Hodgkin Lymphoma

Vincristine is included in the combination therapy regimens for Hodgkin lymphoma, which include ABVD (Adriamycin, Bleomycin, Vincristine, and Dacarbazine) and OEPA/COPDAC variants in paediatric cases. Its addition allows for increased cytotoxic synergy at G2/M cell cycle blockade with limited additive marrow suppression. Most patients at early stages now have above 90% overall survival, and vincristine is still tolerable to low-intensity regimens in an effort to limit late effects in children and adolescents.

In blood, vincristine is a stalwart in the CHOP (Cyclophosphamide, Doxorubicin, Vincristine, Prednisone) regimen by which, to date, the world is still standard for diffuse large B-cell lymphoma (DLBCL) and all other aggressive lymphomas. By incorporating it with rituximab (R-CHOP), it is said to give over 70% 5-year overall survival among intermediate-risk patients.

Due to the metaphase specificity of vincristine, it increases the efficiency of DNA-damaging chemotherapy agents like cyclophosphamide and doxorubicin by causing cells to arrest in metaphase and to accumulate genotoxic stress. This also allows quite low hospitalisation demand with weekly administration for outpatient treatment, which is key in sustaining compliance and continuity in treatment protocols for lymphoma.

Neuroblastoma and Wilms' Tumour

Vincristine is involved in other vital roles aside from haematologic oncology. Childhood solid tumours, including neuroblastoma and Wilms' tumour, where multiagent induction with cyclophosphamide, doxorubicin, and cisplatin includes vincristine for tumour debulking before surgical resection and autologous stem cell transplant in case of high-risk neuroblastoma. Aggressive regimens usually include vincristine in both induction and consolidation, and since its addition, response rates have significantly improved[24].

In Wilms' tumour, vincristine-a regimens established by the National Wilms Tumour Study Group usually include dactinomycin and doxorubicin. It is used in both favourable histology stage I-III disease and higher-risk subgroup diseases, in which it reduces the risk of relapse after nephrectomy. Minimal marrow toxicity enables it to be included in nephroblastoma protocols that require intensive postoperative treatment without compromising haematologic recovery[25].

Cumulative vincristine exposure in both diseases is also closely monitored because of the risk for VIPN in young children. Different centres include age-based or genotype-guided dose caps in their efforts to reduce the incidence of long-term neurological sequelae, which is now the trend[13].

Vincristine in Combination Regimens

Vincristine is rarely used strictly as a monotherapy but usually finds its greatest role through combinations with cell-cycle stage-specific agents or otherwise exploiting biological weaknesses. Unique combinations involving vincristine against two cancers, ALL and NHL, include combinations with S-phase agents (methotrexate, cytarabine) and DNA-disrupting agents (anthracyclines) because of the ability to induce G2/M arrest and subsequent apoptosis. R-CHOP and Hyper-CVAD regimens exemplify such combinations with vincristine strategically layered in mechanistic consideration of tumour heterogeneity and clonal evolution.

Vincristine is also currently being studied in combination with anti-targeted drugs, particularly monoclonal antibodies such as rituximab (anti-CD20), inotuzumab ozogamicin (anti-CD22), and blinatumomab (CD3/CD19 bispecific T-cell engager).

The advantage of these combinations is that they would allow lower doses of vincristine while retaining relevant anti-tumour efficacy, thereby decreasing vincristine-related neurotoxicity and potential development of resistance.

Vincristine also acts in regimens of immunotherapy empowerment, whereby, interfering with microtubules, it will collide with immune checkpoint blockade or T-cell therapies disrupt antigen presentation and immunogenicity of the tumour. A summary of preclinical data shows that vincristine might amplify antitumour activity with PD-1/PD-L1 inhibitors by interfering with the intracellular trafficking of ligand; however, clinical evidence remains ongoing

The Role of Vincristine in Paediatric Oncology

Vincristine is a succinct antineoplastic and is one of the most widely used chemotherapeutic agents for malignant lesions in paediatrics. Its established strong antimitotic activity and relatively milder myelosuppressive action make vincristine effective and very clinically used in virtually all forms of childhood malignancies. It is now a standard agent included in induction and maintenance treatments for acute lymphoblastic leukaemia (ALL), Hodgkin and non-Hodgkin lymphomas, Wilms' tumour, rhabdomyosarcoma, neuroblastoma, and embryonal tumours. The therapeutic effect derives from preferentially killing – by this agent – actively replicating tumour cells while allowing the high-dose delivery of other agents without synergistic bone marrow toxicity[26].

Patients with acute lymphoblastic leukaemia (ALL) usually receive weekly doses of vincristine during induction, consolidation, and delayed intensification; its role as one of the principal drugs for cytoreduction at diagnosis and maintaining suppression of minimal residual disease (MRD) during remission maintenance. Retrospective analyses conducted by cooperative groups like COG, BFM, and St. Jude have shown that vincristine contributes to greater than 90 percent of remission rates for children with standard-risk ALL, with five-year event-free survival rates usually above 85 percent[27]. Increasing pharmacogenomic markers, such as *CEP72* and *CYP3A5*, are being put into action on personalising how high or low the dose should be to avoid/minimise VIPN yet allow the medication to still be effective.

This again makes its centrality in the paediatric lymphomas, including CHOP-based regimens for Hodgkin lymphoma and some non-Hodgkin types, OEPA (vincristine, etoposide, prednisone, and doxorubicin), and COPDAC (cyclophosphamide, vincristine, prednisone, and dactinomycin). In this regimen, vincristine adds its own damage to DNA and immunomodulatory drugs that induce mitotic block during a given phase of the cell cycle, thus deepening and prolonging the response. Its particularly favourable characteristics in terms of pharmacodynamics and tolerability make it an attractive agent for developing paediatric regimens that are oriented to cure instead of maintaining long-term quality of life.

Unfortunately, with VIPN, chronic and permanent in some cases appearing late, this surely proves the biggest problem for the paediatric oncologist administering and using vincristine; it occurs in 30% to 50% of children receiving standard doses. The syndrome is presented by paresthesias, absence of deep tendon reflexes, foot drop, and constipation. Furthermore, young children lose it through immature neuronal repair systems and differences in the metabolism of vincristine. Current standard practice includes neurological assessments, age-adjusted dosing, and new genotype-driven approaches to dose reductions.

To augment the delivery of vincristine in a paediatric setting, several formulations of liposomal vincristine have been assessed or are being investigated for portable application (VSLI). This is accompanied by increased circulating times and concentrations of drug within an agreement with a possible reduced neurotoxicity through an assumed avoidance of exposure to the free drug in peripheral neurones. This report has been accomplished in adult relapsed ALL, while ongoing trials are in progress, mainly in the paediatric population, on safety, dosing, and comparative effectiveness[28].

Finally, vincristine is also part of the multimodal protocols prescribed to children treated with radiotherapy, surgery, stem cell transplant, or immunotherapy. High-risk neuroblastoma, for instance, includes vincristine in tandem high-dose regimens pre- and post-transplant; in rhabdomyosarcoma, vincristine becomes an adjunctive to the backbone chemoradiation in terms of intermediate and high-risk conditions. Sooner or later, flexibility and broad functionality will always be the mainstay drug in paediatric cancer treatment paradigms.

Limitations and Challenges

But vincristine is not without limitations, despite its established use for many malignant diseases. Clinical

constraints are posed in the use of vincristine by a multitude of factors, including dose-limiting toxicities, a risk of resistance, and a nontargeted nature resulting in substantial collateral effects with toxicity. In addition, resistance mechanisms that arise in tumour cells are another big hurdle to the utility of vincristine. Given these compelling limitations, continued research is warranted for devising ways of improving this treatment approach or alternate formulations.

Neurotoxicity (Peripheral Neuropathy)

Peripheral neuropathy is the most severe dose-limiting toxicity due to vincristine, being reported in 30%-60% of patients, with larger proportions in children and those receiving cumulative doses above 6 mg/m². VIPN presents as symmetric distal sensory and motor neuropathy and is usually accompanied by areflexia, gait impairment, and functional loss of fine motor control. In advanced stages, it becomes chronic or remains irreversible, particularly in children[29].

The underlying mechanism of VIPN essentially involves vincristine-mediated microtubule destabilisation in the axon, which interferes with the transport of vesicles and mitochondria along the neuronal axis. Following that, altered transport leads to degeneration of the axons, mitochondrial swelling, local hypoxia, and Wallerian-like neurodegeneration. At the same time, recent insights into vincristine's contribution to calcium dysregulation and oxidative stress in peripheral nerves have strengthened its neurotoxicity[15,17] (Fig. 3).

Current approaches for VIPN management remain mostly symptomatic, using gabapentinoids or duloxetine, with varying efficacy. No Food and Drug Administration (FDA)-approved medications currently exist to prevent or reverse VIPN. Pharmacogenomic screening for polymorphisms of *CEP72*, *ABCB1*, and *CYP3A5* is now being utilised to personalise dosing of vincristine in paediatric oncology. In particular, patients with CEP72 T/T genotypes have been shown to be at increased risk for VIPN owing to heightened sensitivity to microtubule destabilization[3]. Currently, the guidelines recommend an age-based dose cap, active neurologic monitoring, and alternative scheduling (*e.g.* every second week instead of weekly) to decrease cumulative toxicity.

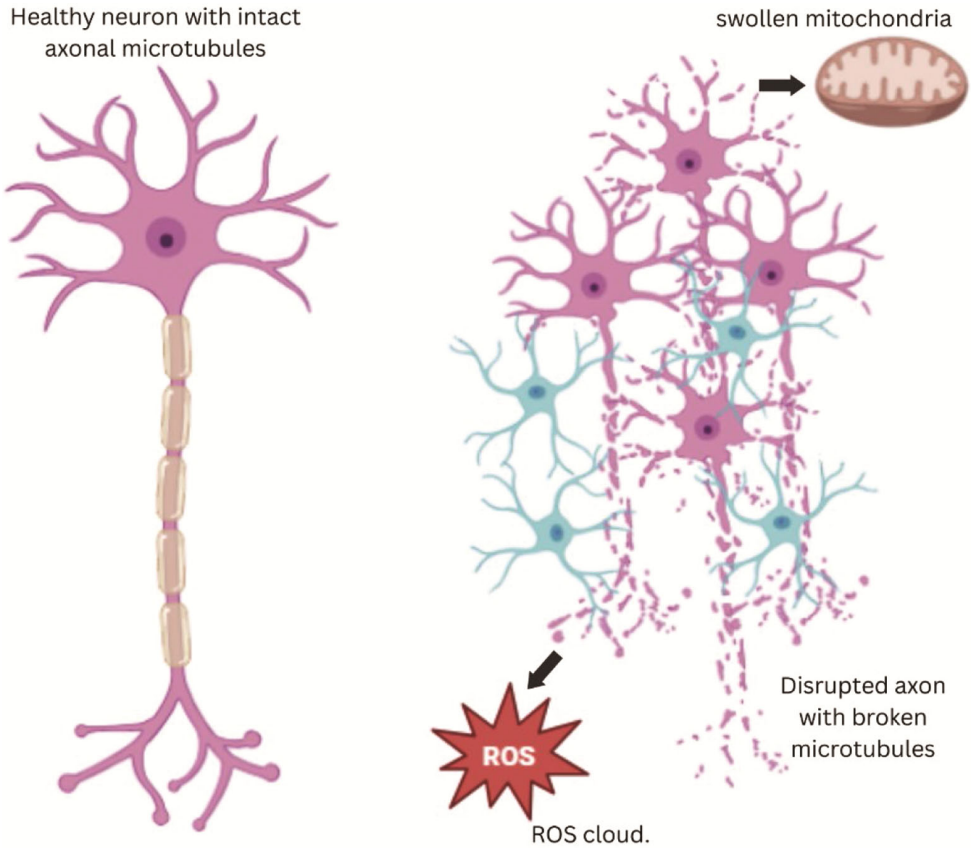

Fig. 3 — Vincristine alters the neuronal microtubule structure to make it impossible for axons to develop transport dysfunction triggering bioenergetic deficits and generation of reactive oxygen species-induced damage

Myelosuppression

The myelosuppression that occurs with vincristine must not be forgotten, notwithstanding that it is mostly described together with neurotoxicity. Myelosuppression is the suppression of the functions of the bone marrow, resulting in lower counts of red blood cells, white blood cells, and platelets. Clinically, these are manifested as anaemia, neutropenia, and thrombocytopenia, which render the patients susceptible to fatigue, opportunistic infections, and bleeding complications[30].

Vincristine, unlike other chemotherapeutic agents such as anthracyclines or alkylators, usually produces less severe bone marrow suppression when given alone. When given in the context of multidrug regimens, particularly those involving cyclosporin, doxorubicin, or methotrexate, the added marrow toxicity is considerable. The risk, moreover, will be increased by the use of drugs, repeat cycles, baseline cytopenias, or regimens undertaken in young children[31].

In an effort to minimise these risks, the patients are monitored closely through thorough repeated complete blood counts (CBCs) during the duration of treatment. Neutrophil or platelet count drops below a critical level; the adjustment or delay of doses is instituted. In some situations, the administration of haematopoietic growth factors, *e.g*., granulocyte-colony stimulating factor (G-CSF) or erythropoietin-based drugs, to support recovery from bone marrow suppression may be considered in high-risk or relapsed situations. G-CSF can be very beneficial in decreasing the length of neutropenia; however, these benefits should be weighed against the perspective of costs and the possibility of stimulating malignant clones in haematologic malignancies[32].

New strategies are the identification of patients who are most likely to develop chemotherapy-induced cytopenias by using predictive biomarkers. Attempts are under consideration to study the pharmacogenetic variants regulating clearance and the marrow sensitivity of vincristine to personalise regimens aiming for reduced marrow toxicity while maintaining effectiveness[33].

Resistance Mechanisms

The development of resistance to vincristine remains a major barrier to long-term remission in haematological malignancies. The initial responses to vincristine-based chemotherapies are usually very strong; however, many cancers, especially acute leukaemia and lymphomas, eventually develop resistance through several molecular mechanisms.

The classical resistance mechanism is the overexpression of P-glycoprotein (derived from ABCB1). It works as an ATP-dependent efflux transporter that actively pumps vincristine out of the cytosol, thereby reducing intracellular concentrations below levels that will reach cytotoxic effects. P-glycoprotein overexpression correlates with treatment failures, early relapses, and poor prognosis in both paediatric and adult leukaemia[34].

Next in line for resistance mechanisms are mutations of β-tubulin, which are altered as a target for vincristine. Isotype switching, lateral βIII-tubulin increased, and point mutations within tubulin genes lower the binding affinity of vincristine, thereby inhibiting the destabilising action of the drug on microtubules. These changes may be "intrinsic" (pre-existing in therapy-naive tumours) or acquired as a result of selective pressure under treatment.

In addition to alterations in targets and transporters, the tumour cells may avoid vincristine-induced apoptosis by escaping the mitotic arrest through checkpoint adaptation and upregulating anti-apoptotic proteins, such as Bcl-2 and survivin, allowing cells to exist even with disruption of the spindle and chromosome aberrations to confer resistance and clonal evolution.

Non-Selectivity and Off-Target Toxicity

Non-selective cytotoxicity is perhaps one of the greatest clinical shortcomings in vincristine. This compound works against neoplastic cells and acts on rapidly proliferating normal tissues. Although the original action of vincristine is the interference of microtubule polymerisation, it can also act on tumours that are highly mitotic; however, dividing cells in the gastrointestinal epithelium, bone marrow, and hair follicles will be affected indiscriminately. As a result, many side effects such as nausea, vomiting, mucositis, and alopecia are usually reversible; however, these very side effects can contribute significantly to patient comfort and compliance disturbances[4].

More troubling, however, is the vincristine toxicity in tissues outside the classical mitotic range, foremost among them being peripheral nervous system cells. Neurones divide relatively infrequently but maintain axonal transport with microtubule integrity. By interfering with these structures, vincristine produces peripheral neuropathy, which is one of the most

frequently occurring debilitating toxicities with the drug. It reveals that vincristine does not exhibit exactly selective action on dividing cells but acts upon any system requiring dynamic microtubules[10].

Moreover, suboptimal heterogeneous biodistribution of the drug together with the inability to discriminate between malignant and normal tissue also contributes to off-target toxicity. With improved supportive care and symptom control, these toxicities continue to hold bad quality of life and, in some cases, induce dosage reductions at the expense of the antitumour effect.

Current developments in targeted delivery systems such as antibody drug conjugates (ADCs) and tumour-targeting nanocarriers are aimed at enhancing such specificity by making vincristine only delivered to the malignant cells and, hence, lowering the systemic exposure. However, this technology is still in developmental stages, and vincristine's lack of selectivity remains a clinical challenge within regular settings.

Pharmacokinetics and Dose Limitation

Compounding this profile is the difficult pharmacokinetics of vincristine, which poses other problems to its effective and safe use. It is mainly metabolised through the liver via cytochrome P450 enzymes, in part *CYP3A4* and *CYP3A5*, and has a long terminal half-life ranging from 19 to 155 h depending on the hepatic function and the patient's age[35]. This variability places patients with compromised liver functionality at risk of build-up of the drug in the body, increasing toxicity and complicating the dose regimen required.

In addition, patients with impaired liver function have a significantly impaired clearance of vincristine and, hence, have increased systemic concentrations with the associated risk for toxicity, particularly neurotoxic effects, as well. Therefore, it is suggested that dosing may be modified based on serum bilirubin concentration and liver enzyme markers to mitigate the side effects. The simultaneous use of other hepatotoxic drugs or inhibitors of CYP3A4, including azole antifungals, can also augment the vincristine toxicities[17] (Fig. 4).

Besides metabolism, vincristine is also fighting low penetration through the blood-brain barrier (BBB), which seriously limits its efficacy against central nervous system (CNS) neoplasms. Though generally effective against systemic haematologic malignancies, vincristine's concentrations remain subtherapeutic within the cerebrospinal fluid (CSF) and yield little therapeutic gain in diseases with CNS involvement such as CNS-positive ALL or primary CNS lymphoma[36].

In an endeavour to overcome this hurdle, intrathecal chemotherapy is carried out routinely with other agents like methotrexate or cytarabine, which are highly permeable across the BBB. However, due to its neurotoxic effects, vincristine is not

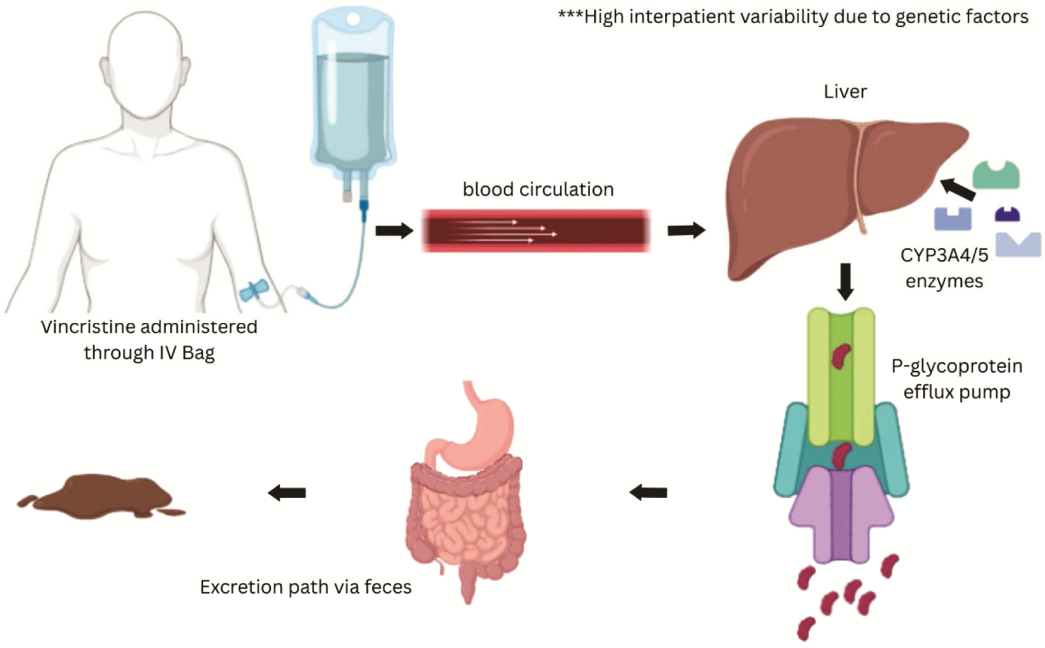

Fig. 4 — After intravenous administration, vincristine undergoes hepatic metabolism via *CYP3A4/5* and is subject to efflux by P-glycoprotein transporters, with elimination primarily through biliary excretion

recommended for use intrathecally, as it could induce lethal neurotoxicity when directly injected into the CNS. Innovations are being studied, including liposomal formulations, transferrin-modified nanoparticles, and BBB-penetrant analogues, to improve the penetration of vincristine into the CNS. Yet these remain largely in an experimental state, and vincristine's limited CNS activity still limits its use in CNS-involved haematological malignancies[1].

Strategies to Overcome Challenges

While vincristine has certainly proven to be a valuable weapon in the arsenal against multiple cancers, it comes with side effects that have motivated the development of different strategies towards the improvement of vincristine in terms of efficacy and toxicity profiles. The areas being tackled include neurotoxicity dose-limiting to vincristine, possible resistance mechanisms, and enhanced selectivity towards cancer cells. Various approaches, including liposomal formulations, synthetic analogues, and advanced drug delivery systems, have emerged as suitable means for overcoming these limitations and hence improving the therapeutic potential of vincristine.

Liposomal Vincristine (*e.g.*, Marqibo)

In terms of the management of vincristine dose-limiting toxicity, the liposomal formulations, namely liposomal vincristine sulphate injection (VSLI), marketed as Marqibo®, are the most important innovations. In this formulation of vincristine, the drug is encapsulated in sphingomyelin–cholesterol liposomes, modifying the drug's distribution and prolonging circulation time to preferentially accumulate in tumour tissues and reduce systemic exposure, particularly to neurotoxic sites[37].

Such a delivery system is designed to minimise exposure to the peripheral nerves and bone marrow, thereby ameliorating neurotoxicity and myelo-suppression. Clinical studies have demonstrated that liposomal vincristine is characterised by better pharmacokinetic stability, having a longer half-life and prolonged therapeutic plasma levels compared to standard vincristine. These characteristics translate into superior efficacy in relapsed or refractory haematologic malignancies, ALL, and aggressive lymphomas[26].

In patients who develop vincristine-related neuropathy, Marqibo retains efficacy and permits a cytotoxic drug to be used with good benefit-risk ratios. However, decreasing toxicity is tempered by accessibility and high cost, both of which hinder use, and optimisation of Marqibo use in combination regimens is still ongoing[23].

Synthetic Analogues with Reduced Toxicity

To limit the adverse effects associated with the use of vincristine, active attempts have been made to synthesise and semi-synthesise those compounds that bear some anticancer efficacy, with ameliorated neurotoxicity and greater monotherapy. This concerns structural modifications on a scaffold derived from Vinca alkaloids, especially at the indole moiety and, in the end, the catharanthine ring system, so as to tune interactions with microtubules while limiting off-target binding[27]. One such analogue vinorelbine (Table 3) has been clinically effective in treating NSCLC and advanced breast cancer with milder toxicity compared to vincristine in some clinical settings. Less toxicity of vinorelbine is likely due to its comparatively lower binding affinity toward neuronal tubulin, which makes it a superior choice for painful conditions with pre-existing peripheral neuropathy or for cases suspected to be at high risk for developing it[12,13].

Vinflunine, a fluorinated derivative of vinorelbine, represents another candidate presently under evaluation in patients with urothelial carcinoma and haematologic malignancies. In early-phase studies it has demonstrated favourable metabolic stability and considerable safety. These synthetic analogues as a whole represent a viable approach to maintaining the efficacy of vinca alkaloids while selectively suppressing their neurotoxic and marrow-suppressive effects.

Table 3 — Production and Cost Comparison of Vinca Alkaloids

Parameter	Vinblastine	Vinorelbine	Vinflunine
Production Type	Natural extraction	Semi-synthetic	Advanced semi-synthetic (fluorinated)
Source Material	*Catharanthus roseus*	Plant-derived precursors	Vinorelbine intermediate
Process Complexity	High	Moderate	Very high
Yield Efficiency	Very low	Moderate	Higher
Scalability	Limited	Improved	High
Production Cost	High	Moderate–high	High

There are additional new candidates being evaluated besides approved analogues, including vindesine, 4'-deoxyvinblastine derivatives, and tubulin-binding peptides. These rationally designed molecules are using algorithms incorporating structure-activity relationships (SAR) and in silico modelling to optimise tubulin interaction and cellular uptake[28].

Targeted Drug Delivery Systems

Targeted drug delivery systems have appeared to overcome the limitations of vincristine by enhancing specificity toward malignant cells with fewer toxicities. Among these, nanoparticle-based carriers seem to be very promising systems whereby vincristine could be encapsulated in polymeric nanoparticles or liposomes, micelles, or dendrimers, allowing administered release and prolonged circulation and specific tumour accumulation via a phenomenon called the enhanced permeability and retention (EPR) effect[18]. Another noteworthy point is that such systems have the possibility of achieving efflux-mediated drug resistance.

Particularly relevant in this regard is the circumvention of P-glycoprotein (P-gp) transporters. By sealing vincristine within a delivery matrix and facilitating the intracellular release after endocytosis, nanoparticles disrespect recognition and clearance by efflux pumps and restore sensitivity to cytotoxic effects in resistant tumour cells[38].

Several preclinical studies have consistently demonstrated an increase in antitumour activity and decreased neurotoxicity when vincristine is loaded into nanoparticles in a leukaemia, lymphoma, or neuroblastoma model. Innovations include ligand-functionalised nanoparticles with targeting moieties such as monoclonal antibodies, folate, transferrin, or RGD peptide directed specifically to tumour cell surface receptors such as CD19, CD22, or integrins, thus improving tumour localization[22].

However, several challenges still exist in the potential application, scalability, reproducibility, and clinical translation of these findings. Targeted nano-delivery has very high potential for expanding the therapeutic index of vincristine, especially in drug-resistant and relapsed haematologic malignancies.

Combination with Other Therapeutic Modalities

Very beneficial in therapeutic applications, vincristine can augment the individual potential treatment purposes of other targeted or immunologic agents, especially when dose de-escalation is possible without compromising activity. Such combinations would aim to match dose-dependent toxicities associated with vincristine use by attacking complementary cytotoxic and immune modulation effects. This is the motivation for the use of vincristine with other agents[20].

Clinically, an example of the above phenomenon is observed in a regimen comprising vincristine and the monoclonal antibody directed at the CD20 surface antigen, rituximab, thereby qualifying it for regimens like R-CHOP, among others, directed against non-Hodgkin lymphoma (NHL). It says that it largely increases the response rates and overall survival, which is primarily for diffuse large B-cell lymphoma, through immune-directed cell lysis of $CD20^+$ tumour cells while vincristine disrupts mitosis[38].

Emerging evidence has also been supportive of vincristine towards immunotherapy combinational treatment, which includes immune-specific checkpoint inhibitors like pembrolizumab and nivolumab. Though primarily developed for solid tumours, such combinations are currently being explored in relapsed Hodgkin lymphoma and T-cell lymphomas wherein the immune-suppressive microenvironment associated with the tumour would limit productive cytotoxic efficacy. Early-phase trials indicate that checkpoint blockade may increase tumour immunogenicity and sensitise cells to vincristine-induced effects[28].

Tyrosine kinase inhibitors (TKIs) such as imatinib or dasatinib have been used together with histone deacetylase inhibitors (HDACis) and evaluated using vincristine in preclinical models for leukaemia to overcome resistance and potentiate apoptotic pathways. These combinations steer towards mechanism-guided multimodal therapy, in which vincristine will act as a backbone agent, amplified through precision molecular modalities.

Personalized Medicine Approaches

The incorporation of personalised medicine into vincristine treatment stands as one of the most promising new frontiers within oncology. By tailoring drug regimens to each patient's genomic and transcriptomic and metabolomic profile, the physician can ensure maximum efficacy while minimising side effects.

In particular, pharmacogenomic profiling of genes called into play by vincristine metabolism and toxicity

– such as *CYP3A5, CEP72*, and *ABCB1* – has yielded actionable correlations. For instance, patients with CYP3A5 non-expressor genotypes might have a reduction in vincristine clearance but an increase in neurotoxicity risk; therefore, an intervention with alterations of their given dose is warranted [34]. Similarly, polymorphisms of *CEP72,* a centrosomal gene, also correlate with vincristine-induced peripheral neuropathy (VIPN), especially in children[28].

Personalised dosing algorithms may be implemented to optimise therapy by identifying patients who may pose a poor tolerance or a low response. For patients demonstrating high P-gp expression or mutant β-tubulin isoforms, alternative agents or adjunctive therapies might be suggested to bypass resistance and toxicity. In addition, molecular profiling of the tumour can now predict sensitivity to vincristine. Certain leukaemias harbouring BCR-ABL1 or TCF3-PBX1 fusions demonstrate enhanced sensitivity to vincristine, and those with *TP53* mutations are likely to be chemoresistant and, therefore, require an alternative regimen[39].

With further relevance of omics-based diagnostics in day-to-day oncology practice, there will be a growing patient-specific design of vincristine-based regimens, leading us into an era in which precision oncology identifies new individual uses for once-conventional chemotherapeutics.

Technical Overview of Vincristine Production

Traditional Production Methods

From the leaves of *Catharanthus roseus*, the alkaloids are mainly extracted for vincristine. Because of the low yield of vincristine and other alkaloids, large-scale production is expensive. The extraction also involves cultivation of the plant, which requires land, water, fertilisers, and pesticides. Such factors increase operational costs. Harvesting the plant and then extracting vincristine through solvent-based methods is labour-intensive and time-consuming. Although it is still a widely used method, the inefficiencies during the extraction account for a bulk of production costs.

Alternative Production Methods

Plant-based extraction methods suffer from inefficiencies, and thus other biosynthetic pathways have been investigated. In vitro plant cell cultures, especially those derived from *C. roseus* hairy roots or from dedifferentiated cells, provide a good, controlled environment that enhances the metabolic flux of alkaloid biosynthesis. This method can reduce variability and increase yield, but a robust investment in bioreactor design, aseptic processing, and media optimisation is necessary.

From a futuristic standpoint, genetically engineered microbial platforms can be developed to express the multi-step vincristine biosynthetic pathway in yeasts (*e.g*., *Saccharomyces cerevisiae*) or bacteria (*e.g*., *E. coli*). This approach offers the potential for sustainable and scaled manufacturing free from agricultural inputs while allowing for better upstream process control.

Notwithstanding the efforts that have been made over the years, complete biosynthesis of vincristine by microbial means has not been fully achieved due to its complex 30+ enzymatic steps requiring highly accurate post-translational modifications in many respects. Semi-synthetic strategies where vinblastine-like precursors are being manufactured by microbial fermentation and then chemically transformed into vincristine are considered good transitional solutions and are being aggressively pursued[40].

Even though chemical total synthesis of vincristine is theoretically feasible, it is, however, practically unfeasible because of the chiral complexity of the molecule with more than 12 stereocentres and complex dimers, along with multi-step purification, which is so high that it will not be commercially viable.

Liposomal and Nanoparticle-Based Formulations

Just as the upstream innovations are taking shape, the downstream formulation of vincristine has undergone revolutionary innovations through liposomal encapsulation and nanoparticle-based delivery. These were intended to increase the therapeutic index of vincristine mainly by changing pharmacokinetics, decreasing off-target toxicity, and enhancing localisation in tumour tissue. Liposomal vincristine (like Marqibo) delivers the drug inside sphingomyelin-cholesterol vesicles that, in effect, increase circulation time, decrease metabolism, and increase uptake in tumours while curtailing exposure to healthy cells, resulting in decreased neurotoxicity and myelosuppression such that patients who developed prior intolerance to vincristine can resume therapy[41].

The nanosystem models PEGylated liposomes, polymeric micelles and dendrimer complexes have been created for better understanding needs of controlling the solubility of drugs, release kinetics and distribution in tissues[42].

At present, ground-breaking research is being targeted towards active targeting strategies, wherein surface ligands present on the nanoparticle (*e.g*., anti-CD19, folate, or integrin-binding peptides) can bind to tumour-specific antigens, enabling receptor-mediated endocytosis of vincristine payloads. All these platforms are at varying levels of preclinical and early-phase clinical evaluation.

Economic Assessment

The economic evaluation of vincristine production focuses on raw material costs, manufacturing expenses, and market demand for both traditional and novel formulations of vincristine.

Production Costs

Conventional plant-derived methods still occupy a predominant position mainly because they have gained favour with the regulators and tend to make lesser investments upfront. Nevertheless, it is labour-intensive, resource-heavy, and depends on the vagaries of an agronomic scheme like climate, pest management, or soil fertility. Also, the need for manual harvesting as well as extraction using solvents drives overhead costs upward, especially in regions where labour is costly or stringent environmental regulations exist.

On the contrary, plant cell culture and microbial fermentation provide more uniform yields and potential for automation. However, these methods are more costly to start up at present since they require custom bioreactors, sterile facilities, high energy inputs, and tight process control to avoid contamination and maintain fidelity to the biosynthetic process[20].

Upstream costs were also highly variable. Liposomal and nanoparticle formulations may have clinical advantages, but their manufacture is considerably more expensive because of the highly sophisticated technologies for encapsulation, the quality control assays involved, and cold-chain logistics.

Generally, movement toward biotechnological and superior formulation methods should increase a drug's costs per dose in the short term but may prove economically sound in the longer term due to lower adverse effects, higher success in treatment, and improved adherence among patients.

Market Pricing and Demand

Prices of vincristine are influenced by the interventions moulded along the lines of mass production, from the method of manufacture to the complexity of formulation to regulations governing licensing, distribution, and finally, the use patterns uninterruptedly existent in the schedules of frontline oncology protocols. Sufficiently standard vincristine is considered cheap, with a long history of clinical application and knowledge of the manufacturer. As a result, the price is usually put within the range of $20-$100 per dose, depending on the area of use, manufacturers on record, and the economy of purchasing[11].

The affordable nature and inclusion in multiple first-line chemotherapy regimens such as R-CHOP, HyperCVAD, and ALL induction protocols have rendered vincristine very much indispensable worldwide, particularly to health systems with fewer resources for its therapies. Vincristine, therefore, continues to have demand because of its price and effectiveness against haematologic malignancies like acute lymphoblastic leukaemia (ALL), non-Hodgkin lymphoma (NHL), and neuroblastoma.

While liposomal vincristine Marqibo® is under another story, with reported prices that have varied between $1,000 and $5,000 a dose. This high price is an indication of the sophistication of the design of the liposomal formulation (Fig. 5), which involves complex lipid engineering, sterility validation, and the development of a targeted delivery system[44]. While the improved pharmacokinetic profile along with reduced neurotoxicity are compelling clinical features, the forward use in many regions was stalled, therefore, by economic challenges immobilizing their reimbursement.

The price differential between standard and liposomal vincristine (Table 3) lays bare an entire oncology tension of innovation versus access. In high-income nations, where insurance coverage or national health services can absorb the cost differential, Marqibo may be considered in relapsed or refractory cases. In low- and middle-income countries (LMICs), however, the high price – often reinforced through marketing strategies – becomes a prominent barrier to accessing the expectant formulation on equitable terms clinically.

The demand for vincristine still stands in tandem with the backbone provided by the drug in the chemotherapy protocols used for children and other adult cancers; during recent years, supply chain disruptions due to the halting of manufacture or shortage of raw materials have reaffirmed the significance of the drug and awakened the regulatory

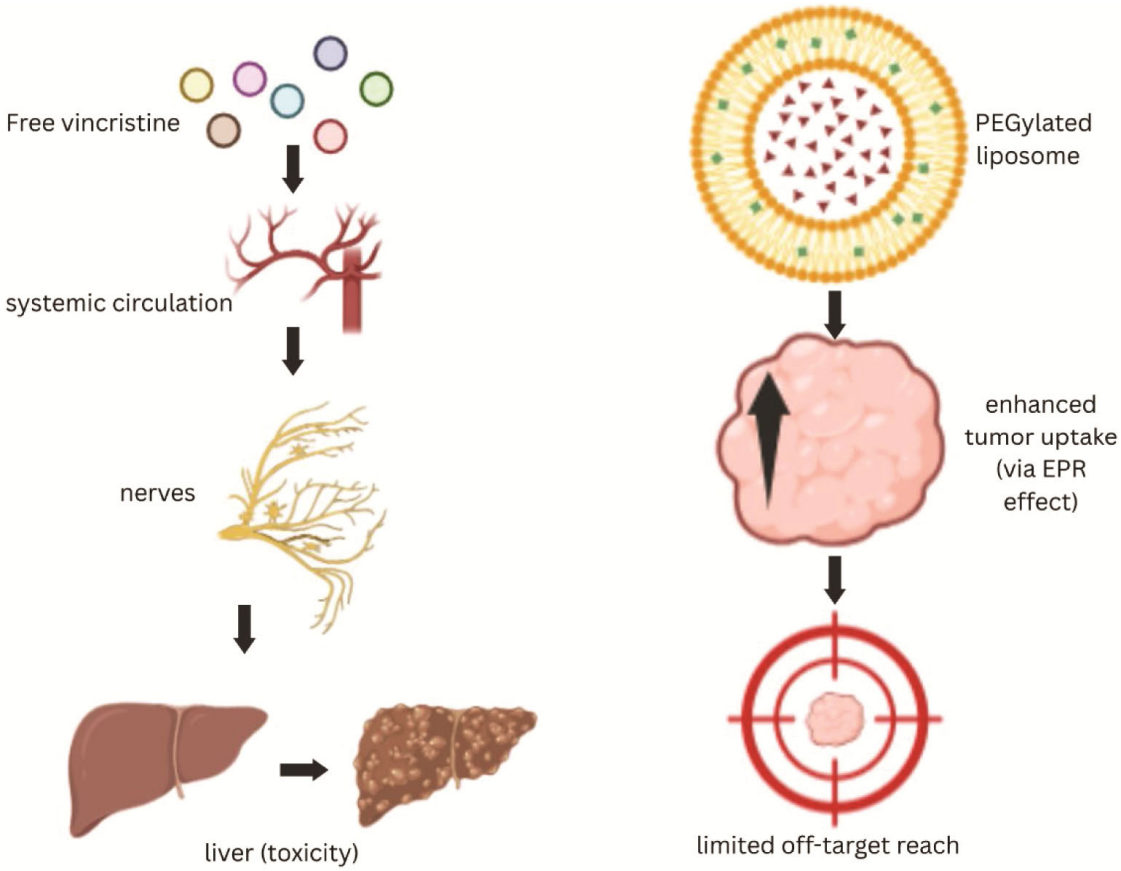

Fig. 5 — Liposomal vincristine (Marqibo) enhances tumor-specific delivery *via* the enhanced permeability and retention (EPR) effect, reducing off-target toxicity compared to conventional free drug formulations

bodies and health systems alike to the necessity of ensuring stable access and anticipated stockpiling.

Therefore, in the years to come, acceptance of advanced formulations like liposomal vincristine or nanoparticle-based systems will probably depend on the objectives of cost-effective analysis concerning long-term endpoints of reduced hospitalisation, less dose delay, and quality of life. Until that time, conventional vincristine will stay the most accepted standard treatment for most world settings, while the premium formulation will be indicated for the high-risk or previously intolerant patient population.

Regulatory and Compliance Costs

Alongside the other factors, the regulatory context for vincristine, with respect to newer formulations which may include liposomal or nanoparticle-operated systems, provides severe financial and procedural hurdles. Obtaining approval from various agencies like the FDA or the European Medicines Agency (EMA) involves conducting multi-phase clinical trials compliant with Good Manufacturing Practice (GMP). These investigations undertake pharmacovigilance systems and toxicological assessments, for which all of them together heavily impact the upfront nonrecurring costs of development[4].

The conduct of clinical trials for advanced formulations is particularly arduous. These have to show good comparability in either efficacy or safety, if not both, to that of conventional vincristine. Such considerations often lead to the need for increased patient population numbers, longer periods of follow-up, and subgroup analysis by stratification. Hence, the requisites from regulators also include extensive documentation covering manufacturing consistency, stability, pharmacokinetics, and formulation-specific behaviour, such as liposome integrity or nanoparticle dispersion.

Beyond even this consideration of costs, compliance efforts continue throughout vincristine approval. Continued advancements of quality assurance and batch release testing, as well as post-marketing surveillance and adaptation to ongoing changes in international regulatory frameworks such as the ICH Q12 lifecycle management, are additional

burdens on advanced vincristine production after it has been given approval.

Sustainability and Environmental Considerations

The cultivation of *Catharanthus roseus* has been associated with high land, water, and pesticide usage. These factors impact the overall carbon footprint of vincristine production. Indeed, the setting of bioreactors for plant cell cultures or microbial fermentation would limit environmental impact; there is no need for large-scale agriculture. However, the energy input needed for biotechnology processes is rather high, thus nullifying part of the environmental advantages[35]. Traditional extraction along with state-of-the-art methods leaves waste products such as solvents, plant tissue residues, or residual chemical toxicants. Efficient systems for waste management and recycling are imperative for the minimisation of vincristine's environmental footprint.

India occupies a significant area with the popular medicinal herb of *Catharanthus roseus*, comprising vast fields, applying fertilisers and pesticides, and consuming much water. All these factors count in the vincristine carbon footprint. Increasing efficiency in vincristine production can be achieved through bioreactors for plant cell culture or microbial fermentation, where large-scale agriculture is avoided. However, high energy input in biotechnology processes offsets a considerable number of benefits in the environmental front[12]. Both these forms of extraction generate a variety of pollutants, including solvents, plant tissue residues, and residual chemical toxicants. For minimising vincristine's environmental footprint, effective waste management and recycling systems are imperative.

Catharanthus roseus has been associated with high land, water, and pesticide usage during cultivation. All these factors are part of the total carbon footprint of vincristine production. Creating bioreactors for plant cell culture or microbial fermentation would avoid the creation of large-scale agriculture and thus limit the environmental impact. The input still needs a huge amount of energy, which offsets part of the advantage gained through biotechnology processes. Traditional and modern extraction methods have some waste to produce, including solvents, plant tissue residues, and residual chemical toxicants. Waste-efficient management and recycling systems are essential for the minimisation of the vincristine environmental footprint.

Cost-Benefit and Return on Investment (ROI)

While upfront costs may be high for available advanced vincristine products like liposomal and nanoparticle versions, long-term returns for these investments may be substantial. The aforementioned drugs decrease incidences of severe neurotoxicity, myelosuppression, and treatment delays by enabling more targeted delivery, and these eventually translate into reductions in hospitalisation rates, needs for supportive therapy, and adherence.

From a payer's point of view, these merits would offset early cost-drug costs and improve cost-effectiveness in the overall evaluation of that drug, especially when regarded from quality-adjusted life years (QALYs) or hospital resource utilisation perspectives. For example, patients in the past limited by a vincristine-induced neuropathy can return to therapy due to the use of liposomal formulations, resulting in improved continuity of treatment and long-term outcomes.

Moreover, the return on investment is dependent on market conditions. The ROI of value-added formulations in high-income markets with favourable reimbursement schemes will be high, as people are always ready to pay for less toxicity and personalised therapeutic options[44]. New markets will probably develop as oncology infrastructure is revamped or established or precision medicine is adopted.

Otherwise, in low- and middle-income countries, where the limits of drug budgets and lack of access to diagnostics are significant obstacles, liposomal vincristine's high costs will hardly gain entry into the market. Thus, ROI highly depends on the degree of manufacturing scalability, the presence of favourable policy incentives, and the capability to lower formulation costs through process innovations.

In sum, while vincristine costs currently remain favourable, the future of vincristine therapy will most likely hinge on the economics of newer formulations, depending on the clinical benefit, regulatory approvals, and adaptability of the healthcare system.

Recent Advances and Future Prospects

Among the effective agents in cancer management, especially in haematological malignancies, is vincristine. Despite its documented efficacy in chemotherapeutic treatment, continuing work is done for the optimisation of properties, like enhancing its efficacy while reducing its toxicities or exploring its new indications elsewhere in therapy (Table 4). Combining vincristine with effective current

Table 4 — Cost Comparison of Different Vincristine Formulations[29]

Formulation	Price Range (per dose)	Cost Factors	Advantages	Disadvantages
Standard Vincristine	$20 - $100	Plant extraction, low manufacturing cost	Cost-effective, widely available	High neurotoxicity, less targeted
Liposomal Vincristine	$1,000 - $5,000	Advanced formulation, liposomal encapsulation	Reduced neurotoxicity, improved efficacy	Expensive, limited availability
Nanoparticle Formulations	$2,000 - $7,000	Nanoparticle encapsulation, high-tech synthesis	Targeted drug delivery, reduced side effects	Expensive, not widely used

treatment strategies for cancer therapy, particularly those directed towards individualised medicine or genomics-guided protocols and combination therapies, is predictive of improving outcomes for patients.

Role in Personalized Medicine

The evolution of personalised medicine has earned the revolution of cancer cure, wherein therapies are individualised based on genetic and molecular characteristics intrinsic to an individual's tumour. Such an approach is becoming more common in vincristine application, particularly in those cancers that give resistance to standard treatment. Genomic profiling of tumours has yielded the discovery of biomarkers that allow predicting sensitivity to vincristine. For instance, mutations in the β-tubulin gene or alterations in the P-glycoprotein expression can predict vincristine resistance, which will enable the clinician to select those patients most likely to benefit from the drug.

Optimised vincristine dosing can be achieved, maximising the potential for therapeutic effectiveness while minimising the hazards related to that effectiveness. Variations in genes identified through pharmacogenomic studies affect the metabolism of vincristine in humans, thus opening a possible avenue for dosage adjustment based on the genetic profiles of patients. The new standards can allow more efficient and safer treatment regimens specifically for patients with unique genetic backgrounds or mechanisms of resistance.

Integration with Genomics-Guided Protocols

Genomic-guided protocols are increasingly favoured in modern oncology, whereby treatment decisions rest on next-generation sequencing-nominated data and tumour-specific molecular drivers. To this end, vincristine is being revisited, especially for haematologic malignancies that harbour microtubule-associated gene alterations, drug efflux transporters, or dysregulated apoptosis pathways[43].

As an example, gene expression profiling has shown that the expression of TP53, BCL2, and ABC transporters that are differentially expressed may affect vincristine sensitivity. Mapping these pathways would allow vincristine to be deployed more selectively either alone or together with other targeted agents to overcome intrinsic or acquired resistance. Furthermore, the increasingly sophisticated genomic data would rationalise combinations where vincristine potentiates activities of agents with BCL-2 inhibitors or PI3K-Akt blockades, inducing tumour cell apoptosis and minimising off-target toxicity[15].

Potential in Solid Tumours

It has long been known that vincristine is one of the mainstay drugs used for haematological cancers, but now the prospects for using it in solid tumours seem to be gaining interest. Solid tumours such as breast cancers, non-small cell lung cancer (NSCLC), and neuroblastomas have not been easy to treat with vincristine because of difficulties in drug delivery to the tumour site and resistance mechanisms. Presently, new formulations of vincristine delivered through liposomal systems or nanoparticles are enhancing distribution into and targeted delivery toward solid tumour cells, offering renewed hopes in the fight against these difficult cancers.

Preclinical studies have noted the efficacy of vincristine when used together with other agents, including immune checkpoint inhibitors, targeted therapies, or other chemotherapeutic agents against solid tumours. For example, vincristine may enhance anti-tumour immunity in conjunction with checkpoint inhibitors such as pembrolizumab so that the combination is not only safer but also more efficacious in patients with solid tumours [16]. Research thus aims to develop strategies to cross the blood-brain barrier (BBB) to treat brain tumours, for which vincristine has shown efficacy but with limited penetration.

Emerging Combinations and Immunotherapy

Vincristine therapy is rapidly changing as immunotherapy creeps into the picture. Vincristine, in addition to its important cytotoxic effects, has immunogenic effects, thus making it a rather hopeful

candidate for combination with immune checkpoint inhibitors (ICIs). Early-phase trials suggested that induction of its immunogenic cell death (ICD) effect might, moreover, augment antitumour immunity and lead to synergy of vincristine with nivolumab or atezolizumab[28].

A number of trials currently undergo evaluation concerning the combination of vincristine with ICIs or kinase inhibitors for both haematological and solid tumour indications. In addition, vincristine is part of bridging regimens for CAR-T, where tumour burden is reduced to optimise the immunological landscape before chimeric antigen receptor T-cell infusion[29].

The incorporation of vincristine into immuno-chemotherapy regimens will likely permit lower maximum cytotoxic dosing requirements and, perhaps, an overall decrease in historically dose-limiting side effects associated with vincristine.

Prospects in Vincristine Development

Advancement of vincristine into a chemically innovative future will be followed by formulation sciences and biological understanding. Work is ongoing to provide vincristine with better specificity for microtubules and low neurotoxicity, coupled with a lowered metabolic profile. In addition, CRISPR-based screens identify key genetic determinants of vincristine sensitivity, bringing with it enhanced patient stratification and development of new combination regimens[44].

Nanotechnology indeed drives innovations in their formulation advances, including such exciting things as stimuli-responsive nanoparticles, TME-activated carriers, and ligand-functionalised platforms. And these innovations will target specific cancers around surface markers of cancer cells, redefining vincristine's application in hard-to-treat solid tumours and central nervous system malignancies.

In the end, vincristine would evolve from being just one among other general cytotoxic agents to being part of specificity-based modern oncological regimens through precision drug development, integration of multiple omics, and its application in rational therapy alignment.

Perspectives

Vincristine's therapeutic odyssey has come to exemplify the prime instance of how cannabiotropic chemotherapy derived from plants assumes an important role in modern medicine. The compound has, for the last more than five decades, formed the backbone of therapy in haematological malignancies, not only due to its historical underpinnings but also adaptive repurposing and reformulation that keep it relevant amid rapid changes concerning oncological paradigms.

As a molecularly targeted antineoplastic agent, vincristine achieves its effects by being a microtubule disruptor that induces mitotic arrest; such a foundation now targets the rapidly dividing cells of cancer. However, dose addressing neurosexopathies, myelosuppression, and exalting multidrug resistance pinched this agent with serious limitations that propelled significant investments in research towards innovative formulations and precision delivery methods. The emerging toolkits in liposomal carriers, synthetic analogues, and nanoparticle-based delivery platforms show not only an attempt towards lower toxicity but also improvements in the pharmacokinetics, selection of tissues, and the therapeutic window of an agent.

Moreover, the integration of vincristine in precision medicine frameworks comprised of pharmacogenomics, tumour profiling, and molecular-guided therapy selection indicates dynamic progression which will redefine legacy agents' place in the treatment of patients with cancer. The current potential for synergistic effects of vincristine with immunotherapeutic agents, including monoclonal antibodies and checkpoint inhibitors, opens it up as situated at the crossroads of cytotoxicity and immunomodulation.

Through this transformative approach, vincristine is being reengineered to suit present therapeutic goals, as it does not fail to blend in with the new agents emerging in cancer treatment. Personalisation, sustainability, and combinatorial effectiveness characterise the direction oncology is taking toward individualised regimens; this means that vincristine has not been replaced by newly discovered agents but rather engineered to meet the newer therapeutic objectives. Refinement of vincristine could rely on innovations in technology, biomarker-informed usage, and adaptive treatment models to ensure that it retains compatibility with both haematological and select solid tumours.

Rather, legacy vincristine is a developing medicine that does not lose clinical significance through scientific reinvention, strategic integration, or translational progress; presently, the challenge is finding ways to maximise vincristine use by

continuing to overcome ever unresolved limitations and expanding its use into a broader spectrum of cancer diseases.

Conclusion

Vincristine has been central to modern chemotherapeutic regimens for the treatment of acute lymphoblastic leukaemia, lymphomas, and other haematologic malignancies. It exerts its action by inhibiting microtubules, leading to metaphase arrest, placing the drug in good standing with proven success in the past over a long time. Its neurotoxicity, restricted CNS penetration, and developing wave of resistance mechanisms have put a stop on the research that is subsequently pursued to maximise benefits while curtailing harm.

Advances in formulation, such as liposomal vincristine, semi-synthetic analogues such as vinorelbine and vinflunine, and nanoparticle-enabled targeted delivery, add substantially to the clinical promise of this drug. In tandem, the transverses of precision oncology allow subtle leverage of vincristine in biomarker-based dosing, genetic stratifications, and genomics-directed combinations. These developments promise not just increased potency of the drug, but also less toxicity and better tolerability from the patient's perspective.

Also, the integration of vincristine into immune-therapy-enhanced regimens and investigations against solid tumours clearly represents an important expansion of its clinical horizon. The studies of vincristine combined with immune checkpoint inhibitors, CAR-T bridging therapies, and targeted kinase inhibitors are clear signals that beyond the already broad frontiers, this drug is gradually veering into landmarks never dreamt of.

In the near future, personalised, multi-agent, and technology-assisted therapy for cancer using vincristine will be on the track of solidifying its status as more than a mere reference chemotherapeutic agent into a truly active partner of 21st-century oncology. The path traced further with ongoing research, investment in newer delivery systems, and incorporation into pharmacogenomically optimised regimens will keep and highly enhance its usefulness, thereby ensuring that vincristine continues to be a key player in the changing therapeutic ballet of cancer.

Conflict of interest

All authors declare no conflict of interest.

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