An updated clinical and clinical trial profile of *Catharanthus roseus*: A peerless medicinal plant

*Accepted 5th September, 2018*

**ABSTRACT**

*Catharanthus roseus* (Apocynaceae), commonly known as the Madagascar periwinkle is a species of flowering plant native and endemic to Madagascar, but grown elsewhere as an ornamental and medicinal plant. This plant is a major source of therapeutic compounds having anticancer activity. The major alkaloids in clinical use for treatment of cancer are vinblastine, vincristine, vindesine, vinorelbine and some more compounds under different phases of clinical trials. Apart from these compounds, about fifty (50) different active compounds having different clinical uses are reported. The present review paper enumerates the therapeutically active compounds, clinical uses and clinical trial profile of *C. roseus* reported from 1950 to 2020. We are of the opinion that this review may help scientists, researchers, Ayurvedic practitioners, pharmacognosists, botanists and students who are active in the field of medicinal plants research.

**Key words:** *Catharanthus roseus*, metabolites, clinical profile, clinical trail profile.

**INTRODUCTION**

*Catharanthus roseus* (syn. *Vinca rosea*), the Madagascar periwinkle, rose periwinkle, or rosy periwinkle plant have been in use for many years as an Ayurvedic and folk medicine. *C. roseus* was recognized in the 1950s to produce different metabolites like vincristine, vinblastine, ajmalicine, serpentine, yohimbine, catharanthine, tabersonine, vindoline, strictosidine and secologanin etc having different pharmacological actions like anti-diabetic, anti-hypertensive and anti-cancer activity etc (Jacobs et al., 2004).

The major alkaloids in clinical use for treatment of cancer are vinblastine, vinorelbine (semi-synthetic derivative), vincristine, vindesine (semi-synthetic derivative) and vinflunine. Vinblastine and vincristine bind to tubulin, causing inhibition of microtubule formation and subsequent arrest of mitosis. Vinblastine and vincristine are used to treat a variety of cancers, including Hodgkin’s lymphoma, lymphoblastic leukemia’s and nephroblastomas. Vinblastine and vincristine are classified as monoterpen indole alkaloidal natural products. From 2008, there was also a new synthetic vinca alkaloid, vinflunine (difluorinated derivative) currently approved in Europe for medicinal treatment (Moudi et al., 2013). All vinca alkaloids are administered intravenously in a rapid bolus or with short infusion and require special attention because they are vessels-sclerotics (Chemoth. com, 2018; Alkaloids, 2018); they are metabolized and excreted by the liver.

Vinflunine (other Name: Javlor) is a novel second-generation vinca alkaloid (Gerullis et al., 2011). Vinpocetine (trade name: Cavinton) is a chemical obtained from the leaves of the lesser periwinkle. It improves cerebral metabolism and memory in animals and humans. In addition, it enhances long-term potentiation, which is linked to memory mechanisms. Furthermore, vinpocetine have anti-convulsant effects and is more potent than several commonly used antiepileptic drugs (Jha et al., 2012).

**THERAPEUTICALLY ACTIVE COMPOUNDS OF CATHARANTHUS ROSEUS REPORTED FROM 1950 TO 2020**

At present, more than 50 alkaloids have been isolated from various parts of the plant (Table 1); of these vinblastine and
Table 1: Pharmaceutical properties of \textit{Catharanthus} alkaloids (Rowinsky et al., 2003).

<table>
<thead>
<tr>
<th>Trade name</th>
<th>Vinblastine</th>
<th>Vinorelbine</th>
<th>Vincristine</th>
<th>Vindesine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mol. Formula</td>
<td>$\text{C}<em>{25}\text{H}</em>{35}\text{N}<em>{4}\text{O}</em>{9}$</td>
<td>$\text{C}<em>{26}\text{H}</em>{34}\text{N}<em>{4}\text{O}</em>{8}$</td>
<td>$\text{C}<em>{26}\text{H}</em>{35}\text{N}<em>{4}\text{O}</em>{10}$</td>
<td>$\text{C}<em>{24}\text{H}</em>{34}\text{N}<em>{4}\text{O}</em>{7}$</td>
</tr>
<tr>
<td>Category</td>
<td>Anti-cancer</td>
<td>Anti-cancer</td>
<td>Anti-cancer</td>
<td>Anti-cancer</td>
</tr>
<tr>
<td>Action</td>
<td>Antimitotin</td>
<td>Mitotic inhibitor</td>
<td>Mitotic inhibitor</td>
<td>Mitotic inhibitor</td>
</tr>
<tr>
<td>Route of administration</td>
<td>Intravenous</td>
<td>Intravenous and (rarely) oral</td>
<td>Intravenous</td>
<td>Intravenous</td>
</tr>
<tr>
<td>Half life</td>
<td>24.8 h</td>
<td>27.7 - 46.3 h</td>
<td>19 - 155 h</td>
<td>24 h</td>
</tr>
<tr>
<td>Protein binding</td>
<td>-</td>
<td>79-91%</td>
<td>75%</td>
<td>65-75%</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Hepatic (CYP3A4-mediated)</td>
<td>Hepatic (CYP3A4-mediated)</td>
<td>Hepatic (CYP3A4-mediated)</td>
<td>Hepatic (CYP3A4-mediated)</td>
</tr>
<tr>
<td>Standard adult dose range (mg/m²/wk)</td>
<td>6-8</td>
<td>15-30</td>
<td>1-2</td>
<td>3-4</td>
</tr>
<tr>
<td>Principal toxicity</td>
<td>Neutropenia</td>
<td>Neutropenia</td>
<td>Neurotoxicity</td>
<td>Neutropenia</td>
</tr>
</tbody>
</table>

The vinca alkaloids are cytotoxic's – they halt the division of cells and cause cell death. During cell division, vinca alkaloid molecules bind to the building blocks of a protein called tubulin, inhibiting its formation. The drugs work during the M-phase of cell reproduction. Tubulin protein normally works in cells to create "spindle fibers" (also called microtubules). These microtubules provide cells with both the structure and flexibility they need to divide and die. They are the structure and flexibility they need to divide and die.

The vinca alkaloids present in its leaves and ajmalicine, in its roots are medicinally important. Under irrigated conditions, about 1.5 tonnes of leaves and 0.5 tonnes of roots on air-dry basis are obtained per hectare (Svoboda, 1961; Kumar et al., 2013; Zenk et al., 1977; Yang et al., 2011; Vijai et al., 2013; Coufal and Farnaes, 2011; Tiong et al., 2013; Barrales-Cureño, 2015; Johnson et al., year). The yield of leaves and roots under rain-fed conditions is 0.75 t/ha each on the air-dry basis. Rs. 25000/- is the cost of cultivation for 1 ha (Vikaspedia, 2018). The following are the various active metabolites isolated from various parts of \textit{C. roseus}:

1) Ajmalicine;
2) Carolina;
3) Carosidine;
4) Catharanthe;
5) Catharine;
6) Catharine;
7) Catharosamine;
8) Catharosamine;
9) Leurocolombine;
10) Leurocristine;
11) Leuroside;
12) Lochnenidine;
13) Lochnericine;
14) Lochneridine;
15) Lochnerine N-oxide;
16) Neoleurocristine;
17) Neoleurosidine;
18) Normacusine B N-oxide;
19) Perivine;
20) Pleuroside;
21) Rosicine;
22) Secologanin;
23) Sitsirikine;
24) Strictosidine;
25) Syringetin-3-O-robinobioside;
26) Serpentine;
27) Vinblastine;
28) Vinleurosine;
29) Tabersonine;
30) Vidolicine;
31) Vinamidine;
32) Vinblastine;
33) Vincamicine;
34) Vincamidine;
35) Vincarodine;
36) Vincristine;
37) Vindesine;
38) Vindogentianine;
39) Vindolicine;
40) Vindolidine;
41) Vindoline;
42) Vindoline;
43) Vindoline;
44) Vinorelbine;
45) Vinpocetine;
46) Vinrosidine;
47) Vinrosidine;
48) Virosine;
49) Yohimbine;
50) 17-desacetoxyvinblastine N'-oxide;
51) Pseudovincaleukoblastine diol;
52) 20'-deoxyvinblastine N'-oxide;
53) 7-O-methylpelargonidin 3-O-(beta-galactopyranoside);
54) 7-O-methylpelargonidin 3-O-[6-O-(alpha-rhamnopyranosyl)-beta-galactopyranoside].

**MECHANISM OF ACTION OF VINCA ALKALOIDS**

The vinca alkaloids are cytotoxic's – they halt the division of cells and cause cell death. During cell division, vinca alkaloid molecules bind to the building blocks of a protein called tubulin, inhibiting its formation. The drugs work during the M-phase of cell reproduction. Tubulin protein normally works in cells to create "spindle fibers" (also called microtubules). These microtubules provide cells with both the structure and flexibility they need to divide and die.
replicate. Without microtubules, cells cannot divide (Chemoth. com, 2018).

REPORTED CLINICAL USES OF CATHARANTHUS ROSEUS

Vinblastine is used for the treatment of Hodgkin’s disease, non-Hodgkin lymphomas, testicarcinomas and sometimes against breast cancer and chorio-carcinomas. Vincristine is used against acute leukemia, Hodgkin’s disease, non-Hodgkin lymphomas, rhabdomyosascomas, Wilm’s tumors in children and breast cancer. Ajmalicine is used for the treatment of hypertension ((Vikaspedia, 2018). Apart from these, various clinical uses are reported for different active constituents isolated from different parts of C. roseus. The following are the some of them:

1) Acetycholinestrase (AchE) inhibitor (Pereira et al., 2010);
2) Anthelmintic activity (Jain, 2011);
3) Antibacterial activity (Goyal et al., 2008);
4) Anticancer activity (Widowati et al., 2013);
5) Antidiabetic activity (Singh et al., 2001);
6) Antidiarrhoeal activity (Hassan et al., 2011);
7) Antifungal Activity (Balaabirami and Patharajan, 2012);
8) Anti-glioma activity (Clinicaltrials. gov., 2018a);
9) Anti-inflammatory activity (Clinicaltrials. gov., 2018b; Medina, 2010);
10) Antimicrobial activity (Patil and Ghosh, 2010);
11) Antimitotic activity (Tafur et al., 1975);
12) Antioxidant activity (Widowati et al., 2013);
13) Antitumor activity (Clinicaltrials. gov., 2018c);
14) Antilucre activity (Nosálová et al., 1993);
15) Antiviral activity (Farnsworth et al., 1968);
16) Cognitive enhancer (Clinicaltrials. gov., 2018b; Medina, 2010);
17) Cytotoxic activity (Siddiqui et al., 2010);
18) Hypoglycemic activity (Vega-Ávila et al., 2012);
19) Hypolipidemic activity (Mukherjee et al., 1995);
20) Larvicidal activity (Panneerselvam et al., 2013);
21) Pupicidal activity (Subarani et al., 2013);
22) Wound-healing activity (Nayak and Pereira, 2006);

REPORTED CLINICAL TRIALS ON C. ROSEUS

Constipation in pediatric cancer patients receiving vinca alkaloids (Clinicaltrials. gov., 2018d)

(NCT Number: NCT01463852; Study type: Interventional; Phase: Early Phase 1; Population: 11; Age: 18 Years and older; Sex: All).

The children with cancer were treated with complex therapies including chemotherapy, radiation, surgical interventions and biotherapy. Treatment with vinca alkaloids and/or narcotics combined with significant lifestyle changes secondary to the disease process can have a negative impact on the child’s bowel elimination status. Constipation can be minimized or prevented as an unwanted side effect of the treatment or disease condition in trying to preserve the child’s health and well-being.

Despite the widespread knowledge that constipation is prevalent in oncology patients, evidence shows that cancer treatment plans often overlook constipation and reflect the lack of consensus for effective assessment, treatment and management. The research literature provides a database for addressing particular aspects of constipation. However, few studies address all the factors that affect bowel function and fewer have recruited pediatric populations.

The Constipation Assessment Scale (CAS) is a valid and reliable measure found to be predictive of the presence and severity of constipation in the adult population; however, it has never been tested in the pediatric population. It is necessary to conduct a pilot study utilizing the CAS tool in children diagnosed with cancer. It is necessary to test the process for evaluating the presence and severity of constipation and the reliability and validity of the CAS tool. The study population will consist of inpatients and outpatients less than or equal to 21 years old, receiving weekly vinca alkaloids and/or narcotics greater than or equal to twice per day for pain management. After the last dose of vinca alkaloid and/or narcotic for a maximum of 6 weeks patients will be followed for 7 days. Patients will be assessed on admission for bowel function and constipation. The admission assessment will include a nursing and nutrition assessment, review of the history and physical, and the administration of the CAS. Subsequent assessments include nursing, nutrition, administration of the CAS, and a patient daily bowel diary.

All patients regardless of participation in the study was prescribed interventions based on the bowel prophylaxis and management guidelines established by the NCI POB staff. These guidelines were generated from validated studies, using Medline’s criteria for scientific soundness and clinical relevance, in the oncology literature as well as, from the experience of the NCI POB staffs.

A study of the effect of vinca alkaloids on c-Jun N-terminal Kinase (JNK) phosphorylation in patients with Chronic Lymphocytic Leukemia (CLL) (Clinicaltrials. gov., 2018e)

(NCT Number: NCT01463852; Study type: Interventional; Phase: Early Phase 1; Population: 11; Age: 18 Years and older; Sex: All).

In this proof-of-principle study, patients with chronic
lymphocytic leukemia (CLL), scheduled to initiate treatment per the recommendations of their primary oncologist, received a single dose of 2 mg of vincristine. The objective is to determine if this single dose will induce rapid cell death in isolated CLL cells.

2 mg Vincristine was administered to the participants intravenously over 5 min. Blood samples were collected from an intravenous line inserted into the contra lateral limb where the vincristine was given, at time zero (pre-vincristine treatment), immediately after vincristine administration (within 2 to 10 min upon completion of administration) and at 1, 2, 4 and 6 h post-vincristine treatment. Patients were at a later date received chemotherapy treatment as prescribed by their primary oncologist.

Within 7 days of vincristine administration, participants received a phone call from the research nurse to discuss potential toxicities. At the time of the initiation of standard chemotherapy treatment, the principal investigator will also meet with the participant to collect information regarding adverse events.

A randomized phase ii trial of oral vinorelbine as second line therapy for patients with malignant Pleural mesothelioma (Clinicaltrials.gov., 2018f)

(NCT Number: NCT02139904; Study type: Interventional; Phase: 2; Population: 200; Age: 18 Years and older; Sex: All).

This study is for patients with malignant mesothelioma of the lungs lining (called pleura) who have had previous chemotherapy with a platinum-based regimen whose disease has progressed. Malignant pleural mesothelioma (MPM) is an aggressive, frequently drug resistant and incurable disease that is increasing in incidence in the UK and worldwide. All patients with MPM will relapse following first line chemotherapy and at present, there is no standard treatment available for patients in the second line setting. The vinca alkaloid chemotherapy drug vinorelbine has shown promising activity in a single arm UK trial. However to date, there has been no randomized evaluation of vinorelbine in mesothelioma in the second line setting. In addition, there have been no trials which have looked at underlying molecular changes in mesothelioma which may predict vinorelbine efficacy; this might allow vinorelbine to be used in patients only where there is a chance of benefit. Studies suggest that vinorelbine requires a gene called BRCA1 (shown to be absent in 38% of mesothelioma cases) in order to induce cell death in mesothelioma. The VIM trial aims to establish whether vinorelbine in patients with MPM helps them live longer and whether the BRCA1 gene is helpful in selecting patients most likely to benefit from treatment.

Patients will be randomized (1:2) to receive either active symptom control (ASC) (which is all supportive care deemed necessary for pain management excluding disease-modifying treatment) or ASC with vinorelbine. Patients will continue vinorelbine treatment until evidence of disease progression (or unacceptable toxicity to the drug or patient withdrawal). If vinorelbine activity is demonstrated we will use the results from this trial to inform the design of a future phase III trial.

Vinflunine plus trastuzumab in human epidermal growth factor receptor 2 (HER2neu) over-expressing metastatic breast cancer (Clinicaltrials.gov., 2018g)

(NCT Number: NCT00284180; Study type: Interventional; Phase: 2; Population: 32; Age: 18 Years and older; Sex: Female).

This research study involves the anti-cancer medication trastuzumab and the investigational drug vinflunine. The purpose of these trials is to see if trastuzumab and vinflunine used in combination or vinflunine alone is effective in the treatment of metastatic breast cancer. If the tumor is HER2neu positive, eligible patients will receive trastuzumab and vinflunine intravenously (IV) every 3 weeks. If the tumor is HER2neu negative, eligible patients will receive vinflunine intravenously (IV) every 3 weeks. Patients whose cancer does not grow or decreases in size may continue to receive treatment until cancer progression. Evaluation of cancer will be every 9 weeks.

Epirubicin and vinorelbine in treating patients with stage ii, iii, or iv breast cancer (Clinicaltrials.gov., 2018h)

(NCT Number: NCT00176488; Study type: Interventional; Phase: 2; Population: 31; Age: 21 Years to 120 Years; Sex: All).

This phase II trial is studying how well giving epirubicin together with vinorelbine works in treating patients with stages II, III, or IV breast cancer. Patients receive epirubicin hydrochloride IV on day 1 and vinorelbine ditartrate IV over 6 to 10 min on days 3 and 17. Patients also received filgrastim (G-CSF) subcutaneously on days 4-14 or pegfilgrastim IV on day 4; For patients with stage IIB (T3, N0), IIIA, or IIIB disease, treatment is repeated every 21 days for up to 5 courses in the absence of disease progression or unacceptable toxicity. For patients with stage IV disease, treatment is repeated every 21 days in the absence of disease progression or unacceptable toxicity.

Blood samples were collected at baseline and after course 1 for research studies. Patients with accessible tumor for biopsy undergo sequential biopsies and core needle biopsies at baseline and after course 1. Tumor tissue samples were used for determination of p53 status by western blot analysis, immunohistochemistry, and DNA sequencing. Microtubule-associated protein 4, p53, while p21/WAF1 expression was analyzed by western blotting.
After completion of the study treatment, patients were followed for 1 month.

**Trial of vinflunine versus alkylating agent in metastatic breast cancer (Clinicaltrials.gov, 2018i)**

(NCT Number: NCT01091168; Study type: Interventional; Phase: 3; Population: 594; Age: 18 Years to 75 Years; Sex: Female).

In metastatic breast cancer (MBC) patients who have already received anthracyclines, taxanes, antimetabolites and vinca-alkaloids and have developed drug resistance to these drugs, therapeutic options are very limited. Alkylating agents showed a modest activity in pretreated metastatic breast cancer. This phase III trial will compare the effectiveness and the safety profile of vinflunine to an alkylating agent of physician choice in MBC patients who have exhausted anthracyclines, taxanes, antimetabolites and vinca-alkaloids.

**Cognitive effects of vinpocetine in healthy adults and patients with epilepsy (Clinicaltrials.gov, 2018b)**

(NCT Number: NCT02011971; Study type: Interventional; Phase: 1, 2; Population: 30; Age: 18 Years to 60 Years; Sex: All).

A pilot study on healthy volunteers and patients with epilepsy was carried out to assess the potential efficacy and safety of different dosages of vinpocetine in improving cognition.

Cognitive problems are common in patients with epilepsy, but there is currently no specific treatment available. Vinpocetine is a chemical obtained from the leaves of the lesser periwinkle. It has been shown to improve cerebral metabolism and memory in animals and humans. In addition, it has been shown to enhance long-term potentiation linked to memory mechanisms. Furthermore, vinpocetine has been shown to have anticonvulsant effects and is more potent than several commonly used antiepileptic drugs (that is, carbamazepine, phenytoin, valproate, oxcarbazepine, lamotrigine and topiramate) in inhibiting both sodium and calcium channels, which control the release of excitatory neurotransmitters that can lead to brain injury. Thus, vinpocetine might offer a unique drug to help cognition in patients with epilepsy. The investigators propose to conduct pilot studies in healthy volunteers and in patients with epilepsy to assess the potential efficacy and safety of different dosages of vinpocetine in improving cognition.

**Vinorelbine for children with progressive or recurrent low grade gliomas (Clinicaltrials.gov, 2018a)**

(NCT Number: NCT01497860; Study type: Interventional;

Phase: 2; Population: 13; Age: up to 18 Years (Child, Adult); Sex: All).

The purpose of this study is to investigate whether weekly vinorelbine treatment can shrink or slow the growth of pediatric low-grade gliomas that have either returned or continue to grow.

Vinorelbine is a semi-synthetic vinca alkaloid that has recently generated interest in patients with pediatric low-grade glioma. It has been specifically synthesized to broaden its therapeutic spectrum and decrease the neurotoxicity associated with related agents.

In this trial, Vinorelbine will be given intravenously once a week for 6 weeks followed by 2 weeks rest (6 of every 8 weeks) for one year. The patients will then be followed for 60 months. Progression free survival is the primary outcome and defined as none of the following: 20% greater increase in the sum of the longest diameter of the target lesion, or a measurable increase in a non-target lesion, or the appearance of new lesions.

**Phase iii study of vinflunine plus methotrexate versus methotrexate alone in patients with head and neck cancer (Clinicaltrials.gov, 2018c)**

(NCT Number: NCT02347332; Study type: Interventional; Phase: 3; Population: 459; Age: 18 Years to 80 Years; Sex: All).

For patients relapsing after platinum-based therapy, few data are available. The current use of cetuximab associated with radiotherapy in localized disease and associated with platinum-based chemotherapy in the first-line setting stresses the need for new therapeutic options at later stages of SCCHN. Vinca-alkaloids demonstrated activity in SCCHN. Vinflunine demonstrated superior antitumor activity to vinorelbine in preclinical animal models. SCCHN based on a clinical review preliminary phase I results of the vinflunine plus methotrexate combination show encouraging antitumor activity and an acceptable safety profile. Therefore, the combination of vinflunine and methotrexate appears to be a promising salvage regimen after platinum failure.

The present study has been designed as a multicenter and randomized phase III study that compares the combination of IV vinflunine with methotrexate to methotrexate alone in SCCHN patients having failed platinum-based therapy.

**Vinblastine, celecoxib and combination chemotherapy in treating patients with newly-diagnosed metastatic ewing's sarcoma family of tumors (Clinicaltrials.gov, 2018j)**

(NCT Number: NCT00061893; Study type: Interventional; Phase: 2; Population: 38; Age: up to 50 Years; Sex: All).
Drugs used in chemotherapy, such as vinblastine, work in different ways to stop tumor cells from dividing so they stop growing or die. Celecoxib may stop the growth of Ewing’s sarcoma by stopping blood flow to the tumor. Combining more than one chemotherapy drug with celecoxib may kill more tumor cells. Phase II trial to study the effectiveness of combining low-dose vinblastine and celecoxib with standard regimens of combination chemotherapy in treating patients who have newly diagnosed metastatic Ewing’s sarcoma family of tumors.

A study of vintafolide in participants with advanced solid tumor (Clinicaltrials.gov, 2018k)

(NCT Number: NCT02049281; Study type: Interventional; Phase: 1; Population: 3; Age: 20 Years and older; Sex: All).

This study evaluates thrice weekly dosing with vintafolide to find the maximum tolerable dose. The primary study hypothesis is that administration of vintafolide to participants with advanced solid tumors will have acceptable safety and tolerability.

Study of vintafolide in participants with progressive adenocarcinoma of the lung (Clinicaltrials.gov, 2018l)

(NCT Number: NNC00511485; Study type: Interventional; Phase: 2; Population: 43; Age: 18 Years and older; Sex: All).

This phase II clinical trial evaluates the benefit from therapy with vintafolide in participants with progressive adenocarcinoma of the lungs.

Vintafolide is a drug that is specifically designed to enter cancer cells through the folate vitamin receptor (FR). Experimental evidence shows that this target receptor is expressed on a significant portion of non-small cell lung cancers. Early clinical evidence in a small number of phase I patients suggests that vintafolide is generally well-tolerated, without many of the side-effects observed in more-standard therapeutic agents. This evidence suggests that vintafolide may be useful as chemotherapy against progressive adenocarcinomas of the lungs. The primary objective of this study is to collect data on clinical benefit produced by therapy with vintafolide.

All participants will undergo imaging with the FR targeting investigational imaging agent etarfolatide (EC20, FolateScan) during the screening period to confirm eligibility for the treatment portion of the clinical trial. Clinical evidence suggests that etarfolatide may be used to identify patients with cancers that express the target receptor. Information about the safety and tolerability of both vintafolide and etarfolatide will be assessed.

Study of vintafolide in patients with advanced ovarian and endometrial cancers (Clinicaltrials.gov, 2018m)

(NCT Number: NCT00507741; Study type: Interventional; Phase: 2; Population: 49; Age: 18 Years and older; Sex: All).

Phase II clinical trial evaluates the benefit from therapy with vintafolide in participants with advanced ovarian and endometrial cancers.

Vintafolide is a drug that is specifically designed to enter cancer cells through the folate vitamin receptor (FR). Experimental evidence shows that this target receptor is expressed in virtually all ovarian cancers as well as, the majority of endometrial cancers. Early clinical evidence in a small number of phase I patients suggests that vintafolide may have antitumor effect in women with advanced ovarian cancer and that it is generally well tolerated.

This evidence suggests that vintafolide may be useful as chemotherapy against advanced ovarian and endometrial cancers. The primary objective of part A of this study is to collect data on clinical benefit produced by therapy with vintafolide. The primary objective of part B of this study is to collect data on the safety and efficacy of vintafolide.

All participants will undergo imaging with the FR targeting investigational imaging agent etarfolatide (EC20, FolateScan) during the screening period to confirm eligibility for the treatment portion of the clinical trial. Clinical evidence suggests that etarfolatide may be used to identify women with cancers that express the target receptor. Information about the safety and tolerability of both vintafolide and etarfolatide will be assessed.

Study of vintafolide for the treatment of recurrent or refractory solid tumors (Clinicaltrials.gov, 2018n)

(NCT Number: NCT00308269; Study type: Interventional; Phase: 1; Population: 32; Age: 18 Years and older; Sex: All).

This is phase I clinical trial evaluating the safety and tolerability of escalating doses of vintafolide in patients with relapsed or refractory advanced tumors. The primary objective of this study is to determine the safety and maximum tolerated dose of vintafolide given by intravenous bolus or infusion. The efficacy of the treatment will also be measured.

This is a dose escalation study of vintafolide administered by intravenous (IV) bolus or infusion during weeks 1 and 3 of a 4-week cycle to participants with solid tumors refractory to current therapies. Vintafolide is a drug specifically designed to enter cells through a folate vitamin receptor. Experimental evidence shows that the target receptor in many human cancers is over-expressed. There are no previous human studies of vintafolide treatment; however, laboratory research (research in test tubes and/or animals) using vintafolide has shown activity against tumors in animals. This activity in animal models
suggests that vintafolide may be useful as chemotherapy against human cancers.

**Satraplatin and vinorelbine in advanced solid tumors (Clinicaltrials.gov., 2018b)**

(NCT Number: NCT01220284; Study type: Interventional; Phase: 1; Population: 27; Age: 18 Years to 75 Years; Sex: All)

Vinorelbine (NVB) and platinum compounds are anticancer agents with broad spectrum of efficacy, clinically and preclinically proven synergism and only partially overlapping toxicities. Combinations with vinorelbine and platinum compounds with limited neurotoxicity are among the most used palliative regimens in a variety of solid tumors, including NSCLC, breast and cervical cancer. The oral platinum analogue satraplatin (SATRA) has been brought into clinical development because of the antitumor activity and toxicity comparable to those of carboplatin, together with a good acceptability of the oral administration. The recent availability of oral formulation of anticancer agents of proven efficacy in some indications is likely to become a valid option that could affect clinical daily management. The oral administration of vinorelbine and satraplatin might represent a reasonable option of palliative treatment in patients with advanced breast cancer, NSCL, GU or GY tumors for which a curative treatment cannot be provided.

**Vincocetine Inhibits NF-κB-dependent Inflammation in Acute Ischemic Stroke Patients (Zhang et al., 2018)**

(NCT Number: NCT02878772; Study type: Interventional; Phase: 2, 3; Population: 60; Age: 18 Years to 80 Years; Sex: All)

Immunity and inflammation play critical roles in the pathogenesis of acute ischemic stroke. Therefore, immune intervention, as a new therapeutic strategy, is worthy of exploration. Here, investigators tested the inflammation modulator, vincocetine, for its effect on the outcomes of stroke. For this multi-center study, investigators recruited 60 patients with anterior cerebral circulation occlusion and onset of stroke that had exceeded 4.5 h but lasted less than 48 h. These patients, after randomly division into two groups, received either standard management alone (controls) or standard management plus vincocetine (30 mg per day intravenously for 14 consecutive days, Gedeon Richter Plc., Hungary).

**A pharmacokinetic and pharmacodynamic study of vincristine in children with leukemia (Clinicaltrials.gov., 2018p)**

(NCT Number: NCT00001689; Study type: Interventional; Phase: 1; Population: 90; Age: Child, Adult, Older Adult; Sex: All)

The pharmacokinetic behavior of vincristine in pediatric patients has not been well characterized. The present study will obtain detailed information on vincristine pharmacokinetics in patients treated for standard risk ALL on CCG protocols 1952/1962. There will be development of a limited sampling strategy and the interpatient and intrapatient variability of vincristine pharmacokinetics in children studied. Thereafter, a correlation between vincristine neurotoxicity and vincristine pharmacokinetics will be vital.

**Platinum resistant ovarian cancer evaluation of doxil and vintafolide combination therapy (Clinicaltrials.gov., 2018q)**

(NCT Number: NCT00722592; Study type: Interventional; Phase: 2; Population: 162; Age: 18 Years and older; Sex: Female)

This is a phase II clinical trial to evaluate the efficacy and safety of the combination of vintafolide and pegylated liposomal doxorubicin (PLD; available in the United States as Doxil® and outside the United States as Caelyx®) as compared to PLD alone.

Vintafolide is a drug specifically designed to enter cancer cells through the folate vitamin receptor (FR). Experimental evidence shows that this target receptor is expressed on virtually all ovarian cancers. Early clinical evidence in a small number of phase I subjects and in a subset of subjects in an on-going single-arm phase II study suggests that vintafolide may have antitumor effect in women with advanced ovarian cancer and it is generally well-tolerated. This evidence suggests that vintafolide may be useful as chemotherapy against advanced ovarian cancer.

Patients at centers with EC20 imaging capability will also undergo imaging with the folate receptor (FR-) targeting investigational diagnostic agent EC20 during the screening period to assess uptake of this agent into tumors. This non-invasive procedure will provide additional information on the utility of EC20 imaging to identify subjects with the FR molecular “target” before treatment with vintafolide therapy.

**A study of vintafolide given alone or with chemotherapy in participants with advanced cancers (Clinicaltrials.gov., 2018r)**

(NCT Number: NCT01688791; Study type: Interventional; Phase: 1; Population: 37; Age: 18 Years and older; Sex: All)

This trial will be conducted in three parts. Part A is a dose escalation trial followed by a dose confirmation trial in folate receptor (FR) 100% endometrial cancer participants. The primary hypothesis of this trial is that administration
of vintafolide in combination with carboplatin and paclitaxel is safe and tolerable. Part B is a single dose, dose escalation, pharmacokinetic (PK), and QTc interval trial.

The primary objectives include determination of the maximum single tolerated dose of vintafolide and evaluation of the effect of this single maximum dose on the QTc interval. Part C is a weekly dose escalation trial of vintafolide followed by a dose confirmation. The primary hypothesis of this part is that weekly vintafolide has acceptable safety and tolerability in participants with advanced cancers.

CONCLUSION

C. roseus (syn. Vinca rosea, Apocynaceae), is a species of flowering plant, grown and cultivated throughout India as an ornamental and medicinal plant, a source of the drugs used to treat cancer. The plant is widely used in Ayurveda, Siddha and Folk medicine but was recognized in the 1950s to produce different metabolites like vincristine, vinblastine, ajmalicine, serpentine, yohimbine, catharanthine, tabersonine, vindoline, strictosidine, and secologanin etc having different clinical uses. So far, more than 50 different active constituents were isolated from different parts of the plant having different reported clinical uses like anticancer, antidiabetic, antiulcer, antiviral, anti-diarrhoeal, antitumor, antioxidant, antifungal, antioxidant, anti-inflammatory, antimicrobial, antimitotic, antihelminthic antibacterial, cytotoxic, larvicidal, wound-healing and cognitive enhancer activities.

Apart from that, various phases of clinical trials was also carried out on C. roseus. This includes the following:

1) A randomized phase II trial of oral vinorelbine as second line therapy for patients with malignant pleural mesothelioma (NCT02139904);
2) Vinflunine plus trastuzumab in human epidermal growth factor receptor 2 (HER2neu) over-expressing metastatic breast cancer (NCT00284180);
3) Epirubicin and vinorelbine in treating patients with stages II, III, or IV breast cancer (NCT00176488);
4) Trial of vinflunine versus alkylating agent in metastatic breast cancer (NCT01091168);
5) Cognitive effects of vinpocetine in healthy adults and patients with epilepsy (NCT02011971);
6) Vinorelbine for children with progressive or recurrent low grade gliomas (NCT01497860);
7) Phase III study of vinflunine plus methotrexate versus methotrexate alone in patients with head and neck cancer (NCT02347332);
8) A study of vintafolide in patients with advanced solid tumor (NCT02049281);
9) Study of vintafolide in participants with progressive adenocarcinoma of the lung (NNCT00511485);
10) Study of vintafolide in participants with advanced ovarian and endometrial cancers (NCT00507741);
11) Study of vintafolide for the treatment of recurrent or refractory solid tumors (NCT00308269);
12) Satraplatin and vinorelbine in advanced solid tumors (NCT01220284);
13) Vinpocetine inhibits NF-kB-dependent inflammation in acute ischemic stroke patients (NCT02878772);
14) A pharmacokinetic and pharmacodynamic study of vincristine in children with leukemia (NCT00001689);
15) Platinum resistant ovarian cancer evaluation of doxil and vintafolide combination therapy (NCT00722592);
16) A study of vintafolide given alone or with chemotherapy in participants with advanced cancers (NCT01688791), and with some of them completed.

REFERENCES


ClinicalTrials.gov. (2018f). Epirubicin and Vinorelbine in Treating Patients...

Cite this article as:

Submit your manuscript at:
http://www.academiapublishing.org/ajmp