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Review articles

New insights into Vinca alkaloids resistance mechanism and circumvention in lung cancer

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ABSTRACT

Nowadays, lung cancer, as a health problem in worldwide, has high mortality both in men and women. Despite advances in diagnosis and surgical techniques of lung cancer in recent decades, chemotherapy is still a fundamentally and extensively useful strategy. *Vinca* alkaloids are a class of important and widely used drugs in the treatment of lung cancer, targeting on the *Vinca* binding site at the exterior of microtubule plus ends. Either intrinsic or acquired resistance to chemotherapy of *Vinca* alkaloids has been a major obstacle to the treatment of lung cancer, which arose great interests in studies of understanding and overcoming resistance. In this review, we focused on the application and resistance mechanisms of the *Vinca* alkaloids such as vinblastine, vincristine, vinorelbine and vinflunine in lung cancer. We reviewed characteristic resistance mechanisms in lung cancer including over-expression of ATP-binding cassette (ABC) transporters P-glycoprotein and structural, functional or expression alterations of β-tubulin (βII, βIII, βIV) which may devote to the development of acquired resistance to the *Vinca* alkaloids; multidrug-resistance proteins (MRP1, MRP2, MRP3) and RLIP76 protein have also been identified that probably play a significant role in intrinsic resistance. Lung resistance-related protein (LRP) is contributed to lung cancer therapy resistance, but is not deal with the *Vinca* alkaloids resistance in lung cancer. Understanding the principle of the *Vinca* alkaloids in clinical application and mechanisms of drug resistance will support individualized lung cancer therapy and improve future therapies.

1. Introduction

Lung cancer is now the common cause of cancer related deaths in both men and women worldwide, which has two major types: small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC) [1]. Roughly accounting for 80–85% of the cases is NSCLC. It was estimated that 1.6 million lung cancer deaths occurred worldwide in 2012, accounting for 19% of all cancer deaths, and the percentage rose to 27% in 2014 [1,2]. The increasing deaths rate indicates the importance and imminence of lung cancer treatment. Among various therapeutic approaches, chemotherapy is a fundamental and extensive treatment in lung cancer. Approximately 40–50% of NSCLC patients with advanced or metastatic stage, are not candidates for curative therapy and mainly depend on treating with systemic chemotherapy [3].

Although the treatment and diagnosis of lung cancer has made great progress in decades, chemotherapy is still the mainstay of therapeutic methods. However, the common problem of chemotherapy is drug resistance which seriously limits cancer therapeutic effect. Drug resistance can be divided into intrinsic resistance (inherent insensitivity to some cancer cells) or extrinsic resistance (due to the course of treatment with genetic or epigenetic changes) [4]. The development of extrinsic resistance in tumor is potentially association with several alterations, including up-regulated drug efflux, mutations of protein isoforms, suppression of apoptosis and the other potential mechanisms have been investigated [5].

The mechanisms of drug resistance as a therapeutic target are not only the key to overcome or block resistance, but also a clinical challenge [6]. Co-administering with inhibitors of ATP-binding cassette (ABC) transporter proteins like P-glycoprotein (P-gp) or multidrug-resistance proteins 1 (MRP1) have entered clinical progression but with limited success [7]. And the synthesis of several novel chemotherapeutic agents with low susceptibility to resistance mechanisms has been non-stopped development [8,9]. On the other hand, to reduce or mitigate the emergence of drug resistance, one of the commonly used methods in clinic is drug combination. For example, a well-tolerated combination of sunitinib, cisplatin and docetaxel followed by

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maintenance vinorelbine in NSCLC patients had the overall response of > 60 months [10].

Vinca alkaloids were first applied into clinical chemotherapy during the 1960s, exerting the anti-tumor effects by interfering with microtubule function and inhibiting angiogenesis. The action mechanism was relating to cause the depolymerization of microtubules and destabilization of the mitotic spindles, ultimately resulting in cell cycle arrest and cell death [11]. The clinical efficacy of *Vinca* alkaloids have been demonstrated in a broad spectrum of cancers by single use or combination, such as hematological malignancies and solid tumors including lung cancer, germ cell cancer, neuroblastoma *etc*.[12,13]. Although *Vinca* alkaloids have significant clinical activity in multiple tumor types, their effectiveness is restricted by drug resistance. The rational and systematic comprehensions of *Vinca* alkaloids in lung cancer will be benefit to the use in clinic, since the *Vinca* alkaloids (such as vinorelbine and vinflunine) will remain a basic chemotherapeutic drug for the treatment of lung cancer, particularly in advanced NSCLC. This review aims at elaborating current mechanisms of *Vinca* alkaloids resistance in lung cancer and suggesting potential ways to circumvention.

1.1. Discovery and clinical application of Vinca alkaloids in lung cancer

Vinca alkaloids, derived from plants (*Vinca* rosea also known as Catharanthus roseus) or semisynthesis, have potent antitumor activities by preventing microtubules polymerization [14,15]. The discovery of the anti-tumor effects of *Vinca* alkaloids was an accidental and lucky story [16]. A folklore about the periwinkle plant suggested that their extracts had oral hypoglycaemic properties. When researchers originally detected the pharmacological efficacy of plant extracts, they noticed that a significant reduction in white blood cells, granulocytopenia and bone marrow destruction in rats instead of anti-diabetic actions. And subsequent studies discovered their ability to prolong the lifetime of lymphocytic leukemia transplantated rats [14,17]. Then the possibilities of *Vinca* alkaloids as potent anticancer drugs were explored and evaluated. By far, there are four major *Vinca* alkaloid drugs in clinical use including vinblastine, vincristine, vinorelbine and vinflunine [18]. The chemical structure of vinblastine and vincristine, which originally are identified from the natural sources, has a catharanthine moiety linked to a vindo line ring, with different substitution in the vindoline group. Vinorelbine and vinflunine, as semisynthetic derivatives of vinblastine, have an eight- rather than nine-member catharanthine ring [19,20]. Among the four members, either vinlastine or vincristine is often used in combination with other anticancer drugs, replacing treatment alone. For example, vinlastine is involved in the treatment of NSCLC as combining administration with cisplatin. Vinorelbine is the most commonly used and extensively tested chemotherapy for lung cancer alone or in combination. The cisplatin-vinorelbine combination had a superior one-year survival rate of 35% compared to 30% for vinorelbine alone and 27% for cisplatin-vindesine; and response-rates were 30%, 14% and 19% respectively [21,22]. The latest one, vinflunine, has higher activities than vincristine, vinblastine, and vinorelbine *in vivo* and develops drug resistance more slowly than vinorelbine [18]. Thus, vinflunine seems to be active and potentially alternative against lung cancer.

Vinblastine, the first member in *Vinca* alkaloid family, was isolated in 1958 [16]. It is usually used in combination with other drugs instead of using alone in lung cancer. Doll et al. reported a phase II clinical study about co-administration of carboplatin and vinblastine in advanced NSCLC, demonstrating that the combination strategy was active in advanced NSCLC patients, however, compared with carboplatin alone had a slight advantage [23]. Vinante et al. evaluated that mitomycin C, vinblastine and cisplatin could be a palliative treatment in advanced NSCLC, with the positive impact on life quality of patients [24]. Recently, three kinds of combined administration regimens (etoposide-cisplatin, paclitaxel-carboplatin or vinblastine-cisplatin) following with radiotherapy in stage III non-small cell lung cancer were assessed by Tabchi and colleagues. Results suggested that the co-administration of vinblastine and cisplatin might be superior to paclitaxel-carboplatin and less toxic than etoposide-cisplatin [25]. Vincristine, the second *Vinca* alkaloids compound, has poor oral bioavailability and is formulated as vincristine sulfate for intravenous administration [26]. Vincristine sulfate (oncovin) was approved by the Food and Drug Administration (FDA) in 1963 and successfully incorporated into chemotherapy regimens [27]. The combination with adriamycin, cyclophosphamide and vincristine (ACV) was an option for second-line or third-line chemotherapy in small-cell lung cancer (SCLC) [28,29]. Moreover, carboplatin/etoposide/vincristine (CEV) or etoposide/vincristine (EV) combination is also an active regimen in the treatment of SCLC. It was reported that CEV chemotherapy regimen produced higher overall response rate and median survival time compared with EV chemotherapy regimen in extensive-stages SCLC, in a prospective randomized phase III trial. The CEV-treated patients with good prognostic factors (e.g., good performance status, younger than 60 years and no distant metastases) had achieved a complete response to first-line therapy [30]. Vinorelbine, as a third-generation *Vinca* alkaloids compound, is available for oral formulation and approved for the treatment of NSCLC. Either a single agent treatment or combination treatment with other anti-tumor drugs are effective in inoperable (advanced) NSCLC [31]. However, vinorelbine also has a heavy risk of adverse reactions to haematological and non-haematological in fragile patients. It was demonstrated that metronomic oral vinorelbine administration (continuous administration of low-dose vinorelbine) in NSCLC might minimize the risk of adverse events [32]. Importantly, vinorelbine has the ability of being a radiotherapy sensitizer in lung cancer. Cisplatin or vinorelbine which acts as a radiosensitizing agent were administered intravenously or orally exhibited a good clinical effect and safety both in young and elderly patients [33,34]. Vinflunine, the newest member of the *Vinca* alkaloids family, was described first in 1998 and approved by the European Medicines Agency (EMA) for treating metastatic transitional cell carcinoma of the urothelium as a second line treatment option [35,36]. Furthemore, vinflunine showed stronger anti-tumor activity than vincristine, vinblastine and vinorelbine against a number of human tumor xenografts and murine tumors *in vivo* [18,37,38]. Maciej et al. illuminated that vinflunine showed similar efficacy end points against docetaxel in advanced NSCLC who had failing treatment with platinum-based chemotherapy in a phase III study. Despite higher rates of some adverse effects (e.g., constipation, anemia, fatigue and abdominal pain *ect.*), vinflunine had manageable overall toxicity profile. These suggested that vinflunine might be a new option in the second-line treatment of patients with stage IIIB/IV NSCLC [39]. Moreover, vinflunine administered in combination with cisplatin as first-line treatment for patients (advanced metastatic NSCLC) in phase I/II trials, demonstrated a tumor response rate of 32.1% and a disease control rate of 79.2% of the treatment patients [40].

1.2. Action mechanisms of Vinca alkaloids

The *Vinca* alkaloids have been widely used for anti-tumor therapy, through interacting with tubulin and microtubules to exhibit their biological effects. Microtubules are composed of a primary skeleton structure of tubulin heterodimers (α- and β-tubulin subunits) [41]. During mitosis, microtubules grow and develop into the mitotic spindle, attaching with chromosomes. Depending on switching between slow growth and rapid shrinkage, microtubules push or pull chromosomes toward the cell poles [42,43]. As shown in Fig. 1 [41,47], the *Vinca* alkaloids bind to the β-subunit of tubulin-dimer at the *Vinca* binding site in the exterior of microtubules. The *Vinca* binding domain on β-tubulin is located closely to the exchangeable GTP binding site. *Vinca* alkaloids generally have two distinct binding sites on microtubules: binding with high affinity to tubulin at the microtubule plus ends, and with low affinity to tubulin along the sides of microtubule surface [44]. *Vinca* alkaloids are classified as destabilizing agents that cause