Expert Opinion on Drug Delivery

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/iedd20

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To cite this article: Nathalie Wauthoz , Rémi Rosière & Karim Amighi (2020): Inhaled cytotoxic chemotherapy: clinical challenges, recent developments, and future prospects, Expert Opinion on Drug Delivery, DOI: 10.1080/17425247.2021.1829590

To link to this article: https://doi.org/10.1080/17425247.2021.1829590

Published online: 14 Oct 2020.

EXPERT OPINION ON DRUG DELIVERY
https://doi.org/10.1080/17425247.2021.1829590

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REVIEW

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Inhaled cytotoxic chemotherapy: clinical challenges, recent developments, and future prospects

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ABSTRACT

Introduction: Since 1968, inhaled chemotherapy has been evaluated and has shown promising results up to phase II but has not yet reached the market. This is due to technological and clinical challenges that require to be overcome with the aim of optimizing the efficacy and the tolerance of drug to re-open new developments in this field. Moreover, recent changes in the therapeutic standard of care for treating the patient with lung cancer also open new opportunities to combine inhaled chemotherapy with standard treatments.

Areas covered: Clinical and technological concerns are highlighted from the reported clinical trials made with inhaled cytotoxic chemotherapies. This work then focuses on new pharmaceutical developments using dry powder inhalers as inhalation devices and on formulation strategies based on controlled drug release and with sustained lung retention or based on nanomedicine. Finally, new clinical strategies are described in regard to the impact of the immunotherapy on the patient's standard of care.

Expert opinion: The choice of the drug, inhalation device, and formulation strategy as well as the position of inhaled chemotherapy in the patient's clinical care are crucial factors in optimizing local tolerance and efficacy as well as in its scalability and applicability in clinical practice.

ARTICLE HISTORY
Received 14 May 2020
Accepted 24 September 2020

KEYWORDS
Aerosol; non-small cell lung cancer; inhalation; lung tumor; metastases; nebulizers; pulmonary delivery; regional chemotherapy; small cell lung cancer

1. Introduction

Inhaled cytotoxic chemotherapy is an approach that is promising for treating localized pulmonary tumors. Pulmonary tumors are usually detected by imaging techniques such as chest radiography, chest computed-tomography after infusion with contrast material and/or positron emission tomography using radiolabelled fluorodeoxyglucose ^{18}F-FDG [1–4]. Diagnosis requires mostly biopsy for histological evaluation including immunohistochemistry [1,3,4]. Biopsy is currently made using fiber-optic bronchoscopy for centrally located lesions and mediastinal lymph nodes, percutaneous computed-tomography guided biopsy for peripheral lung nodules, or after surgical resection [3]. Pulmonary tumors can be either well localized and confined, or dispersed from primary lung cancers or extra-thoracic cancers (i.e. distant metastasis). Non-small cell lung cancer (NSCLC) represents 85% of primary lung cancers and small cell lung cancer (SCLC) represents 15% [1,2]. Distant lung metastases come from primary extra-thoracic cancers such as colorectal, breast, prostate, bladder, head and neck, bone, osteosarcoma, soft tissue sarcoma, melanoma, thyroid, and testicular cancers [3–5]. Some are more localized in the conducting zone of the lung (e.g. the squamous cell carcinoma NSCLC subtype or SCLC) while others are more dispersed in the respiratory zone (e.g. the adenocarcinoma NSCLC subtype or lung metastases) [1,4,6]. Moreover, primary lung tumors (e.g. the adenocarcinoma NSCLC subtype and SCLC) can metastasize in the lung [4,7]. Primary lung cancer is usually caused by exposure to toxic airborne particles (mainly those from cigarette smoke but also industrial substances), which can cause some airway cells to become cancerous and form a tumor [8]. The site of the most common type of bronchogenic tumor is known to be closely related to the site of enhanced deposition of particles (i.e. the carinal ridge, due to impaction) [9–11]. The increase in incidence of adenocarcinoma these last decades is due to changes in smoking habits (i.e. filters, light tobacco cigarettes, and deep inhalation) that have favored distal bronchiolar and alveolar carcinoma at the expense of proximal squamous cell carcinoma (i.e. an incidence of 40% for adenocarcinoma versus 25–30% for squamous cell carcinoma [1]) [12].

Inhalation, or pulmonary drug delivery, is an advantageous route of administration to treat pulmonary disorders. It has become the main route of administration of treatment against asthma or chronic obstructive pulmonary disease (COPD) and is used also to treat some pulmonary infections often encountered in cystic fibrosis or to treat pulmonary hypertension [13,14]. This noninvasive route of administration presents many advantages over systemic deliveries such as the oral or intravenous (iv) routes. These have a favorable pharmacokinetic profile because they limit systemic adverse effects and the first-pass metabolism by concentrating the drug into the site of action. This route of administration allows a lower dose to have a rapid onset and to have the same effect as a higher dose delivered by systemic routes [13,14]. These numerous

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Article highlights

- Discussion of reported clinical trials made with inhaled cytotoxic chemotherapy to highlight the advantages and issues encountered.
- The main technological concerns with the chosen pharmaceutical technology (i.e. nebulizers)
- The latest formulation developments based on dry powders using another pharmaceutical technology (i.e. dry powder inhalers as the inhalation device), highlighting their advantages as well as their potential challenges during pharmaceutical development for:
  - controlled-release formulations presenting lung-retention properties;
  - dry powders based on nanomedicine
- A suggested position for inhaled cytotoxic chemotherapy in clinical practice in view of the recent implementation of immune checkpoint inhibitors in the standard of care.

This box summarizes the key points contained in the article.

advantages have led to this route of administration being evaluated for lung cancer therapy. The drug can be deposited topically, close to or on the tumors, which creates a favorable drug concentration gradient to diffuse into the tumor. Moreover, it allows the tumor to be reached another way than by vascularization, which is the main route in systemic treatments [15]. Some zones of tumors are poorly or non-vascularized, which renders them hypoxic [16]. A hypoxic environment favors invasive and resistant cancer cells or clonogenic cells responsible for tumor cell repopulation [7,16,17]. Moreover, as these zones are more distant from blood vessels, the cells are exposed to a much lower drug concentration from systemic routes even though they need a higher drug concentration to be killed [17–19]. Moreover, drug deposited into the lung is mainly absorbed into the local bloodstream and can also be drained by the lymphatic system [20,21]. This has been proven for a nebulized cisplatin (CIS) solution (dose of 40 mg) delivered to two stage II NSCLC patients two hours before surgery, evaluated by quantification of platinum in their lymph nodes (subcarinal node: 2.09 µg/g) and blood samples (0.13 µg/g) at 90 min post aerosol administration [22]. Therefore, lung deposited drug can follow the same routes as potential invasive cancer cells from a solid lung tumor (i.e. micrometastases) [7,20]. Moreover, depending on their localization, lung tumors are vascularized from either bronchial vascularization from bronchial arteries in the conducting zone (i.e. generation 0 to 16) or from pulmonary circulation in the transitional and respiratory zone (i.e. generation 17 to 23) [23]. As the pulmonary circulation receives the bronchial circulation, the tumors in the respiratory zone can also be reached from local blood circulation by the drug deposited in the larger airways, which represents a second access that can intensify the therapeutic response [21]. Therefore, lung tumors or metastases can be exposed to the drug topically or after it is absorbed or drained into the blood circulation and lymphatic system. In these cases, there is a favorable drug gradient concentration between the target tissue (tumor, lung, lymph node) and the blood (Figure 1).

Cancer is a complex disease characterized by cancerous cells showing phenotypes linked to their ability to adapt to their environment (i.e. genome instability and mutation, deregulating cellular energetics, resisting cell death), to proliferate (i.e., sustaining proliferative signaling, evading growth suppressors, enabling replicative immortality), to modify the immune response (i.e. avoiding immune destruction, tumor-promoting inflammation), and to invade other organs (i.e. by inducing angiogenesis, activating invasion and metastasis) [25]. Moreover, tumors are organized as complex tissues that include a microenvironment favorable to their survival [25]. As cancer presents proliferative and invasive properties with the ability to resist regulatory systems such as the immune system and to adapt to their environment, different modalities are used and combined to treat it [26]. These modalities are surgery and radiotherapy as localized treatments and chemotherapy (i.e. cytotoxic chemotherapy), targeted therapy, hormonotherapy, and immunotherapy as systemic treatments. They are applied and combined according to the histology of cancer, the stage of the disease and the molecular characteristics of cancer cells as well as the performance status of the patient [26]. Cytotoxic chemotherapy is used at almost all stages of the disease to combat the risk of invasion (i.e. metastases, which are the main cause of death in cancer patients [27]). Cytotoxic chemotherapy is nonspecific and non-selective and is mainly delivered by iv injection (perfusion) and sometimes *per os*. These systemic routes of administration distribute the cytotoxic drugs to all parts of the body before reaching the tumor. They therefore inevitably cause severe systemic and dose-limiting toxicities (DLTs) to the patient due to their dose-dependent pharmacological effects [26,28]. Such poorly selective cytotoxic chemotherapies therefore affect rapidly-dividing tissues such as not only tumors but also bone marrow, gastrointestinal mucosa, skin, and gonads. Therefore, these therapies very often induce myelosuppression, nauseas and vomiting, alopecia, and infertility (for women), respectively [26]. Some toxicities are more organ-specific, such as nephrotoxicity for CIS, neurotoxicity for paclitaxel, or cardiotoxicity for doxorubicin [28]. The severity of the adverse effects due to the drug concentration therefore limits the administered dose and induces an interruption of the treatment. Moreover, conventional drugs are mostly used in association, leading to higher efficacy but also to accumulation and/or aggravation of adverse effects, requiring dose adaptations [29,30]. As these toxicities strongly limit the delivered dose, the plasma concentrations are often not high enough to be completely therapeutically effective at the tumor site [26]. This point is crucial. For example, Kim *et al*. have demonstrated that there is a correlation between the platinum concentration in the tumor and the therapeutic response in terms of tumor-size reduction and survival rate for NSCLC patients treated with CIS or carboplatin [31]. Moreover, the severe toxicities require the clinician to interrupt the treatment frequently, mostly for 3 weeks in the case of myelosuppression [17,26]. This treatment interruption is highly recommended to allow bone marrow to recover but is also responsible for tumor cell repopulation [17]. To limit

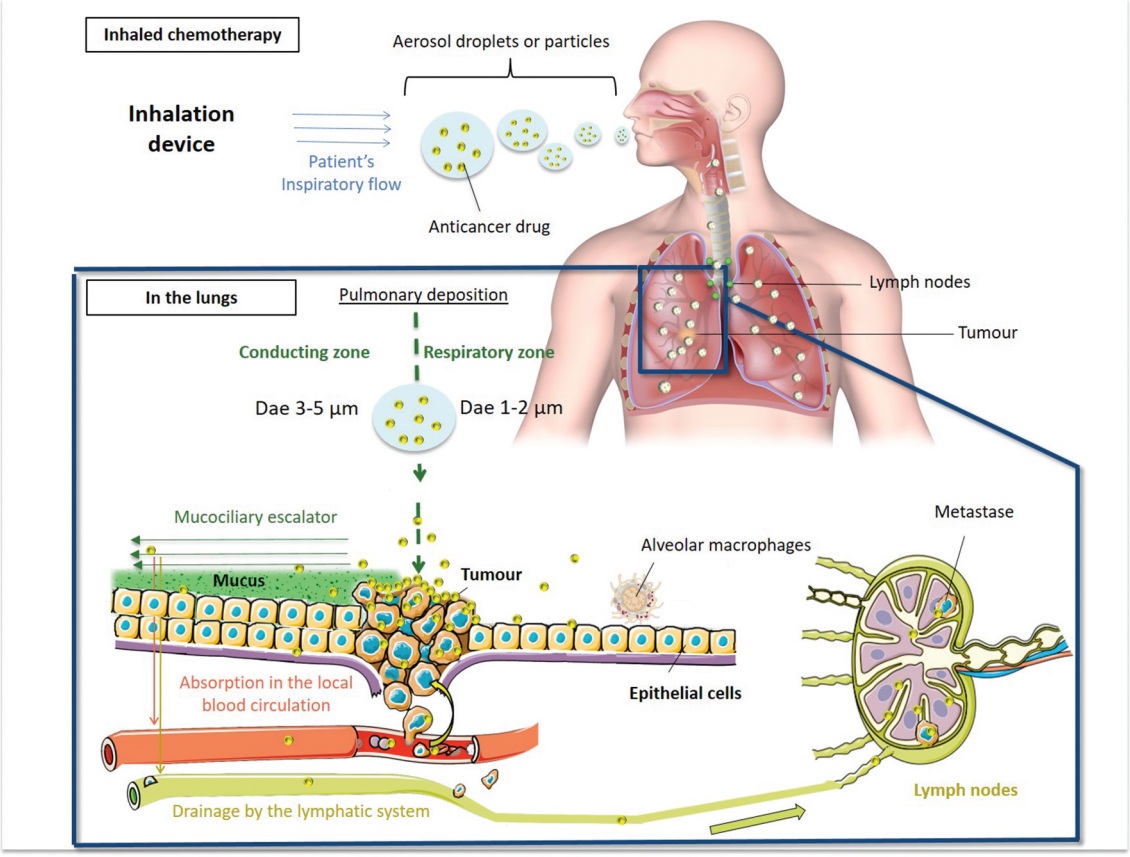

Figure 1. Inhaled cytotoxic chemotherapy – deposition and fate in tumor-bearing lung showing the therapeutic intensification through the locoregional delivery. Dae = aerodynamic diameter. Adapted from Rosière *et al* [89] © 2018 Elsevier Masson SAS. All rights reserved.

tumor cell repopulation, the modification of the dose schedule of a treatment (e.g. dose-dense chemotherapy) can be a promising strategy [17]. That means, for example, giving the treatment more frequently but taking into account that this can also increase its toxicity for normal tissue [17]. Inhaled cytotoxic chemotherapy seems a promising contribution to this kind of strategy by overcoming these different limitations encountered with the systemic route of administration. This is because inhaled cytotoxic chemotherapy is able to increase tumor exposure to the drug(s) with limited systemic toxicities during the interruption period.

Although inhaled gene therapy, targeted therapy, or immunotherapy can be also promising, this review will focus only on inhaled chemotherapy based on cytotoxic drugs (i.e. on small chemical entities with a nonspecific cytotoxic mechanism of action). However, this strategy could be also applied to biotechnological drugs such as antibodies and their fragments, molecularly targeted agents, antisense oligonucleotides, small interfering ribonucleic acid (siRNA), mRNA and DNA inhibitor oligonucleotides, depending on their specificities.

Inhalation of cytotoxic chemotherapy has been evaluated since 1968 and a limited number of clinical trials have been made so far (Table 1) [32–40][**clinicaltrials.gov**]. Although the main advantages in terms of a pharmacokinetic profile with much lower or undetectable systemic side effects have been observed [33–40], technological issues have been highlighted. Cytotoxic chemotherapies are mainly delivered by perfusion in patients. As a simple liquid aqueous sterile formulation, it may be sometimes used directly as a pulmonary formulation delivered through nebulizers [22,33,39]. Nebulizers (including jet, ultrasonic wave, and vibrating mesh nebulizers) are the only inhalation device systems that have been used in pilot studies and clinical trials (Table 1). This inhalation device is able to aerosolize an aqueous liquid formulation into droplets of below 5 µm that are able to be driven into and deposited in the lungs with the patient's inspiration [13]. However, during the aerosolization process, a large part of the aerosol is lost in the device and in the air [13], which is a serious concern for cytotoxic chemotherapy [15,41].

Cytotoxic chemotherapy is composed of at least one hazardous drug, requiring full protective equipment, procedures, and infrastructure before, during, and after preparation and administration to limit the exposure of healthcare personnel [47]. Moreover, the dose of cytotoxic drug needed for it to be deposited in the lungs can be quite large (i.e. one to several tens of mg) and can require a long time of administration by nebulization, which is a second serious concern [35]. Finally, perfusion of some cytotoxic drugs (i.e. 10–30% of chemotherapies in lung cancer therapy [48]) presents pulmonary toxicities (e.g. bronchospasm, interstitial pneumonitis, pulmonary

Table 1. Description of the clinical trials evaluating inhaled cytotoxic chemotherapy adapted from Rosière *et al.* [24]

Drug	Phase	Device, formulation, drug concentration, time of administration	Patients (n), previous treatments status	Dosage	Deposition and/or concentration in the lungs	Most severe local adverse effects and dose-limiting toxicity (dose)	Systemic exposure and most severe systemic adverse effects	Disease response (n or proportion)	References
5FU	Pilot	Ultrasonic wave nebulizer, iv solution, 250 mg/5 mL, 10–15 min/neb. 2/d for 2–3 d/w	Lung cancer eligible for surgery (9) and inoperable with lung metastases (10), Untreated by chemoT or radioT	2.5 mg/kg 2 h before surgery (for operable patients)	Tumor conc. > lung tissue (5–15 times) Conc. in lymph nodes from the hilar > mediastinum	No local side adverse effects	< LOD No detected adverse side effects	Complete response (2/10), partial response (4/10), and no improvements (4/10)	[33]
9NC	I	Jet nebulizer, Liposome dispersion, 2 mg (100 mg excipient) in 5 mL, 30 min/neb. 2 cons. neb./d	Lung cancer and lung metastases (25), No response to previous treatments	6.7 to 26.6 µg/kg/d for 5 cons. d for 1, 2, 4 or 6 w (+ 2 w of rest) 13.3 µg/kg/d 5 cons. d/w for 8 w (+2 w of rest)	4.2- to 10.6-fold higher drug concentrations in BAL than in serum	**26.6 µg/kg/d:** DLT: grade 3 chemical pharyngitis **13.3 µg/kg/d:** Grade 2: cough, bronchial irritation	**13.3 µg/kg/d (0.5 mg/m^2/d)**: C_{max}: 77 ± 39 ng/mL at 1–2 h post inh. vs reported C_{max} ~111 ng/mL at 2 mg/m^2/d per os[42,43] Less toxicities than with *per os* and Grade 2: nausea, vomiting, fatigue, anemia, neutropenia	Partial remission (3) and stable disease (3)	[34]
CIS	I	Jet nebulizer, Liposome dispersion, 1 mg (+23.5 mg excipient)/mL, 20 min/neb. up to 3 cons. neb./ session up to 3 sessions/d (at least 2–3 h between 2 sessions)	Advanced NSCLC (16) and SCLC (1), No response to previous treatments	**Dose escalation:** 1.5 to 60 mg/m^2 1–4 cons. d in 1–3 w (= 1 cycle) for 1–8 cycles	MMAD ± SD: 3.7 ± 1.9 µm, Deposition in the lungs of 10–15% (radiolabelled solution)	**60 mg/m^2**: DLT not reached Grade 3: bronchitis, decreased FEV_1, dyspnea	**60 mg/m^2** : Low plasmatic concentrations (< 1.5 µM) and Grade 4: thrombosis, Grade 3: fatigue	Stable disease (12/18) or progressive disease (4/18)	[35]
	Ib/IIa		Osteosarcoma with lung metastases only (≥ 1 cm) (19) with 8 ≤ 2 cm, previously treated with platinum-based regimens	24 or 36 mg/m^2/2 w (= 1 cycle)	Platinum level in lung and tumor after metastectomy: 200–18 900 ng/g. Vs reported 0–950 ng/g after 150 mg/m^2 3 w post iv or intra-arterial [43] or 0–21 800 ng/g after 150 mg/m^2 intra-arterial[44]	Grade 2: hoarseness	43.6–157.4 ng/ml (30 min post inh. dose) and 47.0–153.5 ng/ml (18–24 h post inh. dose) Vs reported 1600–9500 ng/ml after 100–120 mg/m^2 5 min post iv and 400–3500 ng/ml 24 h post iv[45] and Grade 3: nausea/ vomiting	Complete response (3/19), on tumors ≤ 2 cm with metastasectomy), Partial response (1/19), stable disease (7/19), and progressive disease (8/19)	[36]

(*Continued*)

Table 1. (Continued).

Drug	Phase	Device, formulation, drug concentration, time of administration	Patients (n), previous treatments status	Dosage	Deposition and/or concentration in the lungs	Most severe local adverse effects and dose-limiting toxicity (dose)	Systemic exposure and most severe systemic adverse effects	Disease response (n or proportion)	References
DOX	I	*'Breath-enhanced'* jet nebulizer, Solution pH 3 with 20% ethanol: 16 and 24 mg/mL, 45–60 min/neb.	**Lung metastases (53)**: sarcoma (19), NSCLC (16), colorectal (6), osteosarcoma (4), thyroid (3), miscellaneous (5)	**Dose escalation**: 0.4 to 9.4 mg/m^2 every 3 w (= 1 cycle)	Aerosol particle size: 2–3 µm, Correct deposition in the lung of the radiolabelled solution	**9.4 mg/m^2** DLT: grade 4: respiratory distress/ dyspnea Grade 3: hypoxia; Grade 2: cough, wheezing, dyspnea	C_{max} DOX 47.8 ng/mL and doxorubinol ≤ 7 ng/mL after 5 min post inh. (first sampling time) Vs reported Cmax DOX ~2 000 ng/ml after 75 mg/m^2 post iv[46] and No grade 3–4 systemic toxicities	Partial response (1), stable disease (8) and progressive disease (2)	[37]
DOX			(inh) + CIS (iv) and DOC (iv)	I/II		Advanced NSCLC (43, of which 34 phase II), chemo- or radio-naïve	DOX: 6.0 mg/m^2 (inh, phase II) or 7.5 (inh.) mg/m^2 1–3 h before 75 mg/kg CIS (iv) and 75 mg/kg DOC (iv) every 3 w (= 1 cycle) for 8 cycles	**7.5 mg/m^2** DLT: decrease of > 20% pulmonary function test parameters **6.0 mg/m^2** Grade 3–4 cough and decrease of > 20% pulmonary function test parameters	Systemic toxicities caused by CIS and DOC doublet Grade 3–4:
		constipation, hyponatremia, neutropenia.	Survival (433 d (6.0 mg/m^2) vs 584 d (7.5 mg/m^2, p = 0.58) Complete response (1/24), partial response (6/24), stable disease (13/24) and progressive disease (4/24)	[38]					
GEM	I	Vibrating mesh nebulizer, iv solution, 40 mg/mL, 4–36 min/neb.	NSCLC (11) Stage IIIb (4) or IV (7), All unresponsive to previous chemoT	**Dose escalation**: 1 to 4 mg/kg 1 d/w for 9 w	MMAD: 4.4 µm Deposition in the lungs (42 ± 16%), Homogenous deposition, except in lobar atelectasis	**4 mg/kg** DLT: grade 4: bronchospasm Grade 3–2: cough,	C_{max} (28.1–325.7 ng/mL) after 10 min post inh. Grade 3: fatigue, vomiting	Minor response (1), stable disease (4), progressive disease (4)	[39]

(*Continued*)

Table 1. (Continued).

Drug	Phase	Device, formulation, drug concentration, time of administration	Patients (n), previous treatments status	Dosage	Deposition and/or concentration in the lungs	Most severe local adverse effects and dose-limiting toxicity (dose)	Systemic exposure and most severe systemic adverse effects	Disease response (n or proportion)	References
CAR	I/II	Jet nebulizer + 10 liters of O_2, Solution, 150 mg/15 ml, 40 (15 ml) or 50 min (25 ml)	NSCLC (60; 20/group) stage IV, Untreated previously Tumor between 3 and 5 cm	CAR 160–230 mg/d (inh); CAR (iv) 2/3: 320–460 mg or CAR (iv) 3/3: 550–700 mg +DOC (iv) 100 mg/m^2 **GA**: chemoT iv (CAR + DOC on d1) **GB**: chemoT inh CAR 1/3 (d1) and iv CAR 2/3 + DOC (d1) **GC**: ChemoT inh CAR (d1–3) + iv DOC (d1)	MMAD ± SD: 3.7 ± 1.9 µm, Deposition in the lung parenchyma of the radiolabelled aerosol	**GA**: grade 2: irritative cough **GB:** grade 3: productive cough **GC**: grade 3: dyspnea, hoarseness/ voice change, irritating cough, productive cough	C_{max} **GA**: 23.04 mg/L (30 min-first sampling time); **GB** 18.88 mg/L (30 min first sampling time) and **GC**: 7.98 mg/L (360 min) and Grade 3–4: **GA**: grade 3: fatigue, alopecia, rash, anorexia, anemia and neutropenia, **GB**: grade 3: fatigue, rigors, alopecia, anemia, neutropenia; grade 4: anorexia **GC**: grade 3: fatigue, alopecia, anorexia, dysgeusia, mucositis, nausea, pharyngitis, vomiting, neutropenia; grade 4: anorexia, dysgeusia and Neutropenia significantly less frequent in **GC** (35%) than in **GA** (75%) or **GB** (60%) (p = 0.01)	Survival: **GB** vs **GA** (275 ± 13 d vs 211 ± 13 d, p < 0.001) **GC** vs **GA** (250 ± 7 d vs 211 ± 13 d, p ≥ 0.05) Complete response (**GA**:0, **GB**:2, **GC**:1), partial response (**GA**:5, **GB**:6, **GC**:4), stable disease (**GA**:8, **GB**:3 and **GC**:5) and progressive disease (**GA**:7, **GB**:9, **GC**:10)	[40]

5FU, 5-fluoro-uracil; 9NC, 9-nitro-20(S)-campothecin; BAL, bronchoalveolar lavage; CAR, carboplatin; CIS, cisplatin; conc., concentration; C_{max}, maximum concentration; cons., consecutive; d, day; DLT, dose-limiting toxicity; DOC, docetaxel; DOX, doxorubicin; FEV_1, forced expiratory volume in 1 sec; GEM, gemcitabin; inh., inhalation; iv, intravenous; LOD, limit of detection; MMAD, mass median aerodynamic diameter; neb., nebulization; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; SD, standard deviation; T, therapy; w, week.

fibrosis), which has discouraged many clinicians from trying or having confidence in this pharmaceutical treatment approach [15].

However, with technological and pharmaceutical advances and changes in the therapeutic management of lung cancer, new opportunities and pharmaceutical developments are possible for inhaled cytotoxic chemotherapy if some critical clinical and technological factors are taken into account.

2. Clinical and technological concerns – what have we learnt from key clinical trial reports?

Pulmonary tolerance is the major concern when a cytotoxic drug is delivered by inhalation to treat lung tumors. This is first because the drug is cytotoxic, concentrated into the lungs and delivered chronically. Moreover, the lungs of a patient with tumors often present a poor health status, in particular in primary lung cancer due to smoking and/or with an underlying pulmonary disease (e.g. COPD). Therefore, the choice of the drug candidate is crucial to minimize pulmonary adverse effects. So far, the cytotoxic drugs tested by inhalation in clinical trials have been 5-fluorouracil (5-FU) [33], 9-nitrocamptothecin (9-NC) [34], CIS [35,36], doxorubicin [37,38], gemcitabine [39], and carboplatin [40] (Table 1). They presented a relatively safe profile but the most severe toxicities and/or DLT in phase I have always related to the pulmonary tract. Vesicant drugs such as doxorubicin have induced more severe pulmonary toxicities than other non-vesicant drugs such as 9-NC (e.g. grade 4 respiratory distress/dyspnea versus grade 3 chemical pharyngeal mucositis, respectively) (Table 1). Zarogoulidis *et al*. have classified them in terms of pulmonary toxicity as taxanes > doxorubicin > gemcitabine > platinum analogues >5-FU >9-NC [49]. However, some observed pulmonary adverse side effects have been controlled by bronchodilators [39] and/or steroids given before the nebulization session to alleviate coughs and bronchial irritation [34,40]. Other precautions have been applied to minimize side effects, such as rinsing the mouth [33,39] and/or washing the face after the nebulization session [37,40]. Therefore, prophylaxis with inhaled corticosteroids and/or bronchodilators has been proposed when designing a clinical study to decrease the expected adverse pulmonary effects [21].

However, some drugs such as CIS have not reached the DLT in phase 1 due to an administration time that was too long to deliver enough drug to generate the DLT, i.e. 6 h of nebulization over 3 days, with 60 mg/m^2 per cycle [35]. Therefore, the drug dose required to have a cytotoxic response is also an important factor. This drug dose needs to be formulated to be delivered through an inhalation device. The existing inhalation devices able to deliver drug into the lungs are pressurized metered-dose inhalers, nebulizers, dry powder inhalers (DPIs) and soft-mist inhalers [13]. Pressurized metered-dose inhalers and soft-mist inhalers are reservoir-based inhalers able to deliver only low drug dosages (i.e. less than 1 mg) [13,14]. Therefore, only nebulizers or DPIs are able to deliver the large drug dosages (i.e. higher than 1 mg) [13,14] required for inhaled chemotherapy based on cytotoxic drugs to act on cancer cells and tumors. Aerosol formulations are very device-specific and very technically challenging [13,50]. As nebulizers require an aqueous liquid formulation, some clinical trials have used directly the medicine used for the iv route (e.g. aqueous solutions of water-soluble drugs such as 5-FU (50 mg/ml) [33], gemcitabine (40 mg/ml) [39], or carboplatin (10 mg/ml) [40]) (Table 1).

These aqueous liquid formulations are mostly solutions, but can also be dispersions (e.g. liposomal) or suspensions of fine solid particles that are aerosolized into 1–5 µm droplets by jet, ultrasonic, or vibrating mesh nebulizers [13]. Usually, 5 ml of liquid take 10–20 minutes to aerosolize by nebulization (i.e. a range from 0.2–0.3 [35] to 0.4–0.5 mL/min [40] in clinical trials). Therefore, the drug dose and solubility are important factors in terms of the administration time. For poorly water-soluble drugs, some formulation strategies have been used such as co-solvents or pH adjustment to increase solubility (e.g. 20% ethanol and pH 3 for doxorubicin [37] to increase drug solubility to 16–24 mg/ml in comparison with 2 mg/ml for the iv medicine). However, following the physicochemical properties of the drug, lipophilic drugs (log P > 0) such as doxorubicin (log P of 0.65) will be easily cleared by absorption since they are dissolved, while hydrophilic drugs (log P < 0) can take more time to be absorbed (e.g. CIS (log P of −2.19), gemcitabine (log P of −1.24), or 5-FU (log P of −0.89) [50]. For example, a short T_{max} has been observed for doxorubicin (5 min, which is the first sampling time) and longer T_{max} have been observed for gemcitabine and carboplatin (10 min post-administration and at 360 min, respectively) in clinical trials (Table 1). This phenomenon can impact the lung residence and therefore the therapeutic concentration that is effective against tumors or (micro)metastases.

Therefore, formulation strategies need to be developed to increase the lung residence while maintaining acceptable lung tolerance, as poorly or non-biodegradable materials in the lungs can compromise pulmonary function [50]. With this aim, liposomal dispersions have been developed for CIS (1 mg/ml as the iv medicine) to sustain the release into the lung, even though 40–50% of total CIS is released from the liposomes during the nebulization process [35]. This strategy has also been used for the poorly water-soluble drug 9-NC to solubilize the drug (0.4 mg/ml), stabilize the lactone ring for 9-NC [51], and sustain the drug release. *In vitro* results showed that 32.5% was released in 1 h and 90% after 24 h using a dialysis-based method. This *in vitro* release was also confirmed by a sustained retention *in vivo*, with a 3.4- and a 4.73-fold higher lung area under the curve (AUC) for the liposomes in comparison with the intratracheal or intravenous delivery of the solution in mice, respectively [50]. Moreover, a T_{max} between 1 h and 2 h post-inhalation was observed during the clinical trials (Table 1).

In the inhalation field, it is important to note that the choice of excipients is quite restricted [52], which limits pharmaceutical developments and formulation strategies. All the excipients used in the clinical trials are authorized for inhalation but some are at the limit of lung tolerance. For example, pH 3 used for doxorubicin solution is authorized for a nebulization solution but a pH

over 5 is recommended to limit bronchospasm [50]. Moreover, ethanol can also induce some pulmonary irritation, as demonstrated with cyclosporine A [53,54]. Phospholipids and cholesterol used to elaborate liposomes are well tolerated as they are found in body cell membranes and in lung surfactant but they can show some stability issues during nebulization [54,55], as observed with liposomal CIS used in clinical trials [35].

According to the drug dose to be aerosolized and the drug concentration in the formulation, the administration time varied from 30 min (15 min 2 times per day for 5-FU at 50 mg/ml) to up to 2–3 h (20 min/nebulization 3 times per session with 2–3 sessions per day and with a rest of 2–3 h between 2 sessions for CIS at 1 mg/ml) (Table 1). Moreover, the efficiency of the nebulizer in depositing the aerosol in the lung can also vary. For example, in a Ia/IIb clinical trial using a radiolabelled liposomal CIS dispersion from a jet-nebulizer (PARI LC Star nebulizer with PARI filter) in patients bearing lung metastases from osteosarcoma, only 10–15% of the nominal radiolabelled dose of 36 mg/m^2 was effectively deposited in the lungs [36]. However, 43% of the dose was deposited in the lungs when using a vibrating mesh nebulizer aerosolizing a radiolabelled gemcitabine solution [39] (Table 1). Therefore, drug dose, drug solubility, and nebulizer efficiency can be limiting factors in applying this pharmaceutical approach into clinical practice.

Besides these factors, the aerosol production from nebulizers is generated by the combination of air from a compressor and/or an external power source. This leads to air contamination that has required protective equipment (e.g. full barrier protection clothing such as safety glasses, a respiratory face mask, a gown, gloves, cap, and sleeves), procedures, and infrastructure (e.g. a negative pressure room with a depressurized 'tent' or 'cabins' linked to a HEPA system with a rate of 240 to 360 air changes per hour) for healthcare workers in clinical trials [35,40]. Moreover, the nebulizers used in clinical trials have also used different strategies to limit aerosol losses, such as filters to collect exhaled aerosols [35–40], the OncoMyst model CDD-2A, where only mouth-inhalation is possible [34,37,38], or the Pari LC Star [35], which is breath-enhanced to maximize the inhalation of the aerosol during inspiration (Table 1). However, this is not enough to avoid cumbersome infrastructure, equipment, and procedures. It also highlights concerns about management/cleaning of the device after the administration.

Therefore, inhaled cytotoxic chemotherapy delivered by nebulization requires administration in hospital using tailored infrastructures [41], which limits its possible use for repeated administration in ambulatory care patients or at home.

Respiratory function parameters have been specifically considered as inclusion and exclusion criteria in clinical trials of inhaled cytotoxic chemotherapy. Most of these have required that FEV_1 [22,34–38,40], FVC [22,37,38,40], FEV_1/FVC [34], total lung capacity [34], and/or the diffusing capacity of carbon monoxide [34,37,38,40] are equal to or higher than 50% or not below 50% of the reference values to be included in the clinical trials. For others, either FEV_1/FVC need to be equal or higher than 65% [36] or not less than 30% [39] of the reference values, or resting and exercise oxygen saturations should be equal or higher than 90% and 85% [22,37,38,40] respectively. Other clinical parameters are linked to lung cancer parameters. These parameters include a tumor mass median diameter of between 3 and 5 cm or not more than 5 cm, and no induction pleural effusion or atelectasis [22,40] or main or lobar bronchial obstruction [39]. In terms of exclusion criteria, some of which are involve the lung function specifically, some clinical trials have excluded patients presenting complete atelectasis [37,38], asthma [37,38], pneumonectomy [37,38], any previous chemotherapy with bleomycin, mitomycin, or nitrosoureas, or with any pulmonary toxicity [37] or previous thoracic radiation therapy [37,38]. Stage IV COPD, severe uncontrolled asthma, and bullous emphysema or extended bronchiectasis are also contraindicated by some authors due to the risk of decreased lung deposition [49].

Until now, few studies have evaluated the impact of tumors (size, localization, complete or partial conduit obstruction) and/or of the respiratory function on the deposition of aerosol particles in patients bearing lung tumor(s). One scintigraphy study using a ^{99m}Tc derivative as a tracer of the gemcitabine aerosol in tumor-bearing lungs has shown that aerosol deposition is determined by a defect of lung ventilation in the non-ventilated region due to lobectomy or bronchial tumor [39]. This point remains a crucial factor to consider as clinicians are often skeptical about the ability of the aerosol to reach a tumor that has completely obstructed bronchi or bronchioles or is located in a complete obstructed area. Consequently, more studies are needed to evaluate pertinent criteria for including or excluding patients who could potentially benefit from inhaled chemotherapy. Moreover, following the location and dispersion of the tumors, the strategies and challenges in pharmaceutical development – including the formulation strategy and the choice of the device – as well as in determining the position in the standard of care could be quite different.

In terms of clinical concerns, patients evaluated with inhaled cytotoxic chemotherapy have until now mostly been patients at advanced stages and often previously treated with systemic chemotherapies (Table 1). This could limit the response to this kind of locoregional treatment. There have been relative responses, such as 3 complete responses in 19 previously platinum-based-regimen-treated patients with lung metastases between 1 and 2 cm from osteosarcoma with inhaled CIS [36]. There have also been complete (1/24) and partial (6/24) responses for inhaled doxorubicin in chemonaïve patients, which failed the criteria for passing to phase III (i.e. an overall response rate >35%, corresponding to the lower boundary of more than the 17% response rate reported by Schiller *et al*. [29], and associated with an improvement in pulmonary symptoms) [38]. The most promising results were obtained with carboplatin in untreated patients with stage IV NSCLC and with 3–5 cm tumors in phase II [40]. Carboplatin was delivered either by the inhaled and/or intravenous routes, with docetaxel by the iv route (Table 1) [40]. A significant increase in survival times was observed when combining inhaled carboplatin (1/3 of the dose on day 1) and iv carboplatin (2/3 of the dose on day 1) (group B) compared to the

whole carboplatin dose delivered by iv on day 1 (group A) (275 ± 13 days (95% CI 249–300) for group B vs 211 ± 13 days (95% CI 185–236) for group A, p = 0.01)) [40]. The lower success of inhalation of carboplatin alone (group C) (250 ± 7 days (95% CI 238–363) could be due to the fractionation of the dose with the nebulizer (i.e. 1/3 of the dose/day for 3 days) leading to lower plasmatic platinum concentrations obtained during the first 4 or 6 hours for group C in comparison with group A or group B, respectively) [40]. Moreover, 2/20 complete and 6/20 partial responses were observed for group B in comparison with 0/20 complete and 5/20 partial responses for group A (Table 1), which represents a response of 40% vs 25%.

Until now, all clinical trials using inhaled cytotoxic chemotherapy have remained in phase II [**clinicaltrials.gov**]. A total of four phase II trials of aerosolized liposomal 9NC have been completed but no data have been reported, i.e. for lung metastases from Ewing's sarcoma, in combination with temozolomide (completed in 2009, NCT 00492141), for NSCLC patients at any stage (completed in 2007, NCT 00250068), for metastatic or recurrent endometrial cancer (completed in 2007, NCT 00249990), or from metastatic or recurrent cancer from the endometrium or lung (completed in 2005, NCT 00277082). A phase II trial for liposomal CIS for delaying/preventing pulmonary relapse in osteosarcoma patients in complete surgical remission following one or two prior pulmonary relapses recently completed in 2018 (NCT 01650090) but no data have been published yet. Azacitidine was recently tested in phase I (completed in 2018, NCT 02009436) for stage IV or recurrent NSCLC patients, which showed no DLT or adverse effects but also no objective response (stable disease for 3/8) [56].

3. New pharmaceutical developments to overcome technological concerns

As explained and detailed previously, the choice of drug is crucial before beginning pharmaceutical development of an inhaled form. This choice is in terms of the dose required to provide the therapeutic effect as well as in terms of potential pulmonary toxicity. After this, the choice of inhalation device and formulation strategy is crucial in terms of applicability. The formulation strategy will depend on the drug physicochemical properties and the choice of excipients and will aim to dissolve and sustain the drug in the lung to expose the tumor to the therapeutic drug concentration while limiting the toxic drug concentration to the lung.

Excipients in an inhaled formulation have to be well tolerated by the respiratory tract. Therefore, all novel excipients, i.e. those not authorized for inhalation, need to be stringently evaluated in terms of local tolerance profile [52]. Endogenous components, generally recognized as safe (GRAS), and authorized excipients for inhalation must be privileged when choosing excipients for DPI formulations [52,57].

To overcome the concerns highlighted in the previous section related to the use of nebulizers to deliver cytotoxic drugs, new pharmaceutical strategies have been developed using DPIs as the inhalation device. As the aerosol formulations are very device-specific, they cannot be transposed from one device to another without requiring new development [13,58,59]. The pharmaceutical development of a dry powder and an aqueous formulation for inhalation drastically differ. In general, development is more challenging technically for a dry powder for inhalation in comparison with a simple aqueous solution for nebulization [13,58,59]. Moreover, the scale-up capabilities of the process used to prepare the formulation must be considered strongly in order to scale up successfully the laboratory-scale production to the manufacturing of clinical batches and a marketed product [50].

3.1. Dry powder inhalers as more appropriate inhalation devices to deliver cytotoxic chemotherapy

As ~40% of currently marketed drugs and up to 75% of drug candidates in research and development [60], cytotoxic drugs are mostly poorly water-soluble compounds. Cytotoxic drugs require a dose of one to several tens of mg to deposit in the lungs and, as hazardous drugs, need to be inhaled though a device that prevents air contamination. DPIs, and in particular mono-dose DPIs, seem to be more appropriate than nebulizers for these different points [13,61].

First, DPIs seem to be suitable for confining the cytotoxic drug before and after the dose preparation and administration. With DPIs, the drug aerosol is activated and driven into the lungs through the patient's inspiration only and drug exhalation is negligible (e.g. 0.2% of the nominal tobramycin dose administered through a DPI in healthy subjects [62]). These two characteristics highly limit air contamination. Moreover, as DPIs are small, portable, and not expensive, they can be tailored as disposable devices, hermetically closed after the administration procedure, and picked up at the hospital through a recovery circuit with a possible recycling step to minimize the impact on the environment. Second, a large dose, i.e. one to several tens of mg, can be inhaled within several seconds, with a high fraction deposited in the lungs (e.g. ~30–50% of tobramycin and nominal doses using particle engineering [63,64]). Third, a powder form is more appropriate to formulating poorly water-soluble drugs and presents a higher long-term stability in storage than a liquid formulation.

However, as drug deposition is dependent on the inspiratory airflow through a DPI, it is important to take into account the patient's respiratory performance, inter- or intra-subject variabilities, and their impact on the performance of the dry powder formulation through the selected or designed DPI. Therefore, it is important to minimize the impact of the inspiratory airflow on the performance when designing the dry powder formulation and the DPI [65,66]. A low-resistance DPI should be used as it requires a lower inspiratory effort to reach an airflow that allows good aerosolization, dispersion (deagglomeration), and finally lung deposition of the powder [67]. The patient must be also well trained in the inhalation technique to increase the chance of the therapy's success [68]. A low adherence to or errors in the inhalation technique is often encountered during chronic treatments, which decreases the therapy's success, as observed in asthma and COPD [68,69].

Finally, tumor(s) size and localization can be also a concern when treating lung tumors by oral inhalation. Deposition of aerosol particles (e.g. droplets or dry particles) is dependent on the aerodynamic performance of the aerosol, the lung ventilation (including the inhalation technique), and the lung anatomy [70,71]. The main deposition mechanisms are inertial impaction, sedimentation, and diffusion and depend on these three factors [70,71]. In healthy lungs, particles presenting an aerodynamic diameter (Dae) of 1–5 µm are able to deposit in the lung mainly by gravitational sedimentation [70,71]. This happens when and where the airflow is laminar and persists for enough time, i.e. from the bronchioles to the alveolar sacs (generations 4 to 23) [70,71]. Particles presenting a higher Dae and/or in turbulent airflow are deposited by inertial impaction in the upper respiratory tract and in the trachea and bronchi of the lower respiratory tract (i.e. generations 0 to 3) [70,71]. Particles presenting a Dae below 1 µm can be deposited by diffusion due to the Brownian motion in the narrowest respiratory conduits (i.e. the last generations of the lower respiratory tract) or be exhaled during expiration [70,71]. Dae is defined by the geometric particle size, shape, and density of the particle [72]. In terms of ventilation, the more the intensity of the inspiratory flow rate increases through the device, the more it dispersed/deagglomerates the powder depending on the device's dispersion/deagglomeration system. However, it increases also the velocity of the agglomerated and deagglomerated particles in function of their mass that can increase the impaction phenomena. Moreover, the more the inspiratory volume is large and/or the breath holding maneuver is long, the higher the fraction of deposited particles by sedimentation and by diffusion will be. These phenomena explain the conventional inhalation technique recommended for dry powder inhalers that includes a forceful and deep inspiration through the inhaler, followed by a 10 sec breath holding maneuver before a slow exhalation [66]. Finally, the presence of a pulmonary tumor or an underlying disease (e.g. emphysema, atelectasis) can modify the anatomy (e.g. airway constrictions, airway blockage), the lung ventilation, and therefore the aerosol deposition pattern. Studies have been made to evaluate particle deposition in human adult tracheobronchial tree models presenting sidewall or carinal tumors, constrictions, or obstructions [10,11]. A sidewall tumor decreases the flow rate in the downstream branches on the tumor side and increases the flow rate in the downstream branches on the opposite side, with this tendency increasing with the tumor size. A sidewall tumor also increases the deposition efficiency on the tumor for microparticles until the tumor occupies about half of the airway lumen. The deposition efficiency on the tumor then decreases due to a reduction in the flow rate and number of particles entering the diseased branch [10,11]. Particle deposition is mainly on the carinal ridge and on the outside wall of the tumor due to inertial impaction [10]. In contrast, nanoparticles present low and decreased deposition efficiency on the sidewall tumor [11]. A carinal tumor decreases the flow rate in the bilateral medial branches and increases it in the bilateral lateral branches [11]. It also increases the deposition efficiency on the tumor, in proportion to particle size, with a higher impact with microparticles [11]. A constricted area increases the deposition efficiency [11], while a blocked area deviates and enhances the flow rate to non-occulted branches [11]. Here, the deposition fraction decreases in the blocked branch but increases in the non-blocked second bifurcation [10,11]. However, a few particles still deposit at the tumor site even when the branch is completely blocked [10]. This can be explained by the existence of a low positive airflow near the inside wall, which moves particles to the inner tube wall or tumor site [10]. However, these simulations have been made on a small portion of a symmetrical model (i.e. the Weibel model from G3 up to G5 [11] or G6 [10]) using a spherical tumor located in G4 (carinal or sidewall) [11] or one or two sidewall tumors located in G5 [10]. Therefore, it could be useful to make this kind of study on scans of patients bearing lung tumor(s), for example, using functional respiratory imaging technology. This technique is already used to predict particle deposition for diseases such as asthma and COPD [73,74].

Aerosol delivery and lung deposition from conventional DPIs combined to the conventional inhalation procedure are usually nonspecific for targeting a tumor. However, some authors demonstrated *in silico* the ability to increase the deposited fraction of an aerosol on a tumor surface from 5–10% to 35–92% in normal versus controlled conditions, respectively [75]. The deposited fraction in untargeted zones decreased, respectively, from 20–25% to 5–15% which could decrease local adverse effects on healthy tissues [75]. By controlling critical patient's inspiratory parameters (e.g. inspiratory flow rate, inspiratory volume, time during the inspiration and/or moment of the breath hold manoeuver), *in silico* studies demonstrated the ability to adapt aerosol characteristics and delivery parameters [76,77]. 'Smart' inhalers are developed on these bases to target more specifically a zone of the respiratory tract during the inhalation procedure but they require a much higher cost that renders them difficult to use them as disposable devices.

3.2. Formulation strategies for dry powders for inhalation

To be inhaled and deposited into the lung, drug-based particles must present a Dae between 1 and 5 µm (3–5 µm to be deposited in the conducting zone and 1–3 µm to be deposited in the respiratory zone). However, micronized powders are cohesive, with poor flow, aerosolization, and deagglomeration/dispersion properties. Therefore, they can be mixed at a typical drug ratio of 1:67.5 w/w with a lactose carrier that presents a bigger size (usually lactose monohydrate 50–150 µm), acting as a diluent and improving the flow, aerosolization, and dispersion properties of micron-sized drug particles [72]. This strategy is appropriate to and widely used for low drug-dosage forms, such as for asthma or COPD treatments [72]. However, for high drug-dosage forms, carrier-free strategies need to be developed to increase the drug content [57,61]. For these strategies, particle engineering can be used to improve flow, aerosolization, and dispersion properties by changing the size, shape, density, and surface properties of the particles [57,61,78]. The particle engineering is usually performed using 'bottom-up' constructive methods such as spray drying, spray freeze drying, or supercritical fluid technologies, or by 'top-down' destructive methods such as milling or high-pressure homogenization [61]. Until now, spray drying is the most frequently technique in marketed products for inhalation at high drug dosages,

such as tobramycin inhalation powder (TOBI® Podhaler®, Novartis), mannitol inhalation powder (Aridol®/Bronchitol®, Pharmaxis), and colistimethate sodium (Colobreathe®, Teva) [61]. The spray-drying technique allows a solution, dispersion, emulsion, or suspension to be aerosolized and then dried into uniform powder microparticles. A high drug loading in the dry powder for inhalation and a high fine particle fraction (FPF) through the DPI are strongly desired to decrease the total amount of powder for the patient to inhale to be effective and well tolerated in the lung. A large amount of powder could be irritating and lead to coughing [61]. Taking into account the inhalation ability of the patient, the optimal powder load per inhalation needs to be between 10 and 20 mg. Several successive inhalations can be recommended to inhale all the powder from the capsule [61]. However, a large amount of powder can increase the number of maneuvers (e.g. inhaling several capsules), which can increase the potential for the patient to make errors in the inhalation technique [61].

In the case of the manipulation of hazardous drugs such as cytotoxic chemotherapy, powders are more difficult to manage than liquids and require more protection and dedicated expensive infrastructure during the production and packaging of the medicine. Moreover, the pharmaceutical development of inhalation formulations using hazardous drugs is uncommon and not much developed in the academic or industrial fields, which has also limited pharmaceutical developments.

3.2.1. Controlled-release formulations with sustained lung retention properties

In the case of cancer therapy, a relatively large amount of dry powder (i.e. ten to several tens of mg) will be dispersed and deposited in a very short time onto the small surface of the conducting zone (i.e. 2–3 m^2) and onto the large surface of the respiratory zone (i.e. 100 m^2) [54]. To act pharmacologically, the drug must be released and/or dissolved from the powder in the lung lining fluid (i.e. 10–20 mL/100 m^2) before being eliminated by the non-absorptive clearance systems (i.e. the mucociliary escalator in the conducting zone and the alveolar macrophages in the respiratory zone) [54]. As explained and detailed previously, pulmonary toxicity is one of the major risks of inhaled chemotherapy. To minimize this potential issue, it is important to decrease the peak of the dissolved/released drug concentration in the lungs while keeping it within therapeutic anti-tumor concentrations (i.e. above half median inhibitory concentrations of the drug). The main formulation strategies for controlling the drug release and limiting the lung non-absorptive clearance systems are described in Tables 2 and 3, respectively. These strategies are described in depth in excellent reviews [79,80] and book chapters [81,82]. Briefly, the proof of concept of this strategy of sustained and controlled drug release in the context of lung tumors has been demonstrated in preclinical studies [83–87], and the different formulation strategies using micro- or nanoparticles have been well reviewed elsewhere [88].

However, inhalable particle drug delivery systems for lung cancer therapy are either rarely designed for dry powders for inhalation, have used excipients that are far from potentially well tolerated by the lung (e.g. dendrimers, Table 2), present a low drug loading or FPF (i.e. <20%), or have been produced with poorly transposable scaling-up techniques or with poor yields (i.e. <30%).

Therefore, we have chosen to illustrate one development of a dry powder for inhalation that has almost all of the different aspects required to render it technically and clinically applicable (i.e. potentially well-tolerated excipients, a high drug loading and FPF, and using industrial scaling-up techniques with a good production yield) [101–103].

This development has consisted of reducing CIS microcrystals to submicron crystals (800 nm) by high-pressure homogenization and then embedding them into a highly lipophilic matrix of tristearin (TS) using spray drying to control the particle size and the release of CIS. Tocopheryl PEG1000 succinate (TPGS) is at the surface of particles to decrease the impact of the non-absorptive clearance systems [101]. High-pressure homogenization and spray-drying are both easily scalable techniques. Moreover, spray drying presents good yields in lab production (i.e. 45–61%). However, the dry powder production and its characterization have required the use of highly specific procedures and infrastructure to protect the manipulator and the environment, as described in Wauthoz *et al*. and Levet *et al*. [101,104]. TS and TPGS are excipients that are not yet authorized for inhalation. Inhalation of PEG has been demonstrated as safe [105] and PEGylated excipient derived from vitamin E, such as TPGS, is of low potential pulmonary toxicity [106]. TS, as a triglyceride of stearic acid, exhibits potentially acceptable biocompatibility [52,57]. First, the produced dry powders showed a high CIS content, from 50% to 75%. Second, they showed interesting aerodynamic properties, with FPFs (i.e. the percentage of particles presenting a Dae ≤5 µm related to the nominal dose and theoretically able to be deposited into the lung) comprised between 37 ± 2% and 50 ± 6%. Then, *in vitro* dissolution tests in simulated lung fluid after selecting particles showing a Dae below 5 µm showed that a TS matrix is necessary to significantly slow down the CIS release. Moreover, the increase from 25% to 50% of TS in the matrix significantly decreases the CIS release and the burst effect, but with the same CIS release percentage after 24 h (~80%). Moreover, the addition of 0.5% TPGS at the microparticle surface modifies the release profile from microparticles containing 50% TS lipid matrix by increasing the burst effect (20% vs 11% after 2 min) but decreasing the CIS release (44% vs 63% after 6 h and 55% vs 79% after 24 h) [101]. The formulation presenting controlled release properties and an acceptable drug loading (i.e. 50%) was selected for *in vivo* studies in mice [102]. In fact, this drug loading allows delivery of the same CIS dose into the lung (i.e. 10–15 mg of CIS) as during clinical trials using CIS with a total nebulization time of more than 6 h per cycle (i.e. 10–15% of 60 mg/m^2 for a 1.6 m^2 human) [35]; delivery is in3–4 hypromellose capsules filled with 20 mg of dry powder delivered through the Axahaler® monodose DPI (SMB) (i.e. 5 min of inhalation procedure). The Axahaler® DPI was chosen because it can deliver a relative high powder dose from

Table 2. Formulation strategies for a controlled drug release with the type of excipients used, pulmonary tolerance, particle size, feasibility of scaling-up and the most advanced development stage. Adapted from Rosière *et al.* [89] © 2018 Elsevier Masson SAS. All rights reserved.

	Excipients	Pulmonary tolerance	Particle size	Scale-up	Development stage/example (FDA approval)
Liposomes	Lipids, Phospholipids, Aqueous phase	++	50 nm – 5 µm	+	On the market (injectable) e.g. Doxil® (1995) On the market (inhalation) e.g. Arikace™ (2018)
Micelles	Lipids, Polymers, Aqueous phase	±	< 100 nm	±	On the market (injectable) e.g. Genexol® PM (2007, in South Korea) Preclinical (inhalation)
Dendrimers	Polymers (PAMAM, PEHAM)	±	4–20 nm	±	Phase III (vaginal and rectal) e.g. VivaGel® (2006, fast-track status) Preclinical (inhalation)
Polymer-based nanomedicine	Polymers (PLGA)	-	10–250 nm	±	Phase II (injectable) e.g. BIND-014, BIND Therapeutics Preclinical (inhalation)
Polymer-based microparticles	Polymers (PLGA)	-	0.25–5 µm	++	On the market (injectable) e.g. Lupron Depot® (1989) Preclinical (inhalation)
Solid lipid nanoparticles	Lipids, Phospholipids	+	10–250 nm	-/+	On the market (oral) e.g. Cipro® (2004) Preclinical (injectable and inhalation)
Solid lipid microparticles	Lipids, Phospholipids	+	0.25–5 µm	++	On the market (topical cosmetic) Preclinical (injectable and inhalation)

For the pulmonary tolerance, ++ is for very well-tolerated, + is for well-tolerated, observed in humans or in vivo studies; ± is for formulations partly studied in vivo or in vitro or for which some data is missing, – is for formulations with limited tolerance shown in vivo.
For the scale-up, ++, is for easily scalable; +, is for scalable; -/+, scalable depending on the techniques.
PAMAM, poly(amidoamine); PEHAM, poly(etherhydroxylamine); PLGA, Poly(lactic-co-glycolic acid).

Table 3. Example of formulation strategies developed to overcome lung clearance mechanisms (reprinted from Rosière *et al.* [127] © 2019) with permission from Elsevier.

Lung clearance mechanism to be overcome	Strategy	Formulation characteristic or composition	References
Mucociliary clearance	Aerodynamic targeting – deposition in the alveoli	Dae of 1.8–2.8 µm	[90]
	Mucoadhesion	Mucoadhesive agent-based formulations (e.g. chitosan, hyaluronan, HPMC)	[91,92]
Macrophage clearance	Modification of particle size[a]	Large porous particles, Trojan particles, nanoparticles	[79,93,94]
	Modification of particle shape	Varying particle geometric shapes (e.g. spheres, rectangular disks, elliptical disks)	[95]
	Stealth characteristics, surface modification	PEGylation	[55,96]
Physicochemical enzymatic degradation	Encapsulation, complexation, degradation inhibitors	Liposomes, cyclodextrins, protease inhibitors	[55,97]
Drug absorption	Micro- and/or nano-encapsulation of the drug	Micro- and nanoparticles (lipid, polymer-based)	[79,98–100]

Dae, aerodynamic diameter; HPMC, hydroxypropyl methylcellulose; PEG, propylene glycol.
[a]Assuming optimal phagocytosis by macrophages for particles of 0.5–5 µm, and in particular the range 1.5–3 µm.

a capsule, with good dispersion properties but without increasing the airflow resistance [66]. This kind of device presents the lowest resistance to the airflow. Moreover, the formulation has shown low variability between airflows through the device of 40–100 L/min [101]. This low variability is important in terms of the inhalation technique that the patient will be able to use without compromising the drug delivery into the lung. Moreover, this kind of device also presents a high feedback. However, it requires a certain dexterity [66]. Dexterity and safety issues could be solved by including the capsule in the disposable device to avoid capsule-loading by the patient.

Controlled release and sustained retention properties were then confirmed *in vivo* by performing a pharmacokinetic study in healthy mice using a noninvasive endotracheal DP-4 M dry insufflator (Penncentury, USA) and by mixing the powder with an appropriate dry diluent [102]. This study revealed a higher lung exposure due to the controlled release and sustained retention properties of the TS matrix and TPGS in comparison to only controlled TS matrix without TPGS ($AUC_{10min-48h}$ of 6072 ng.min/mg vs 2079 ng.min/mg). These are much higher values than with CIS powder without TS matrix or in solution ($AUC_{10min-48h}$ 1462 ng.min/mg and 1869 ng.min/mg, respectively). This study confirmed the need to escape the non-absorptive clearance systems to expose enough lung tissue to the drug. This was done by adding an appropriate excipient onto the particle surface (in this case TPGS). Moreover, the controlled release and sustained retention formulation decreased 4-fold the blood C_{max} and increased the blood T_{max} (30 min for CIS solution and powder without TS matrix to 2 h). The plasmatic CIS concentration is an indirect reflection of the lung concentration of dissolved/released CIS in the lung fluid as this CIS is able to act pharmacologically and is then absorbed into the blood.

As expected, the controlled release and sustained retention formulation increased tolerance by increasing 2-fold the maximum tolerated dose administered 3 days a week for 2 weeks in healthy mice in comparison to CIS powder without TS matrix (1.0 mg/kg vs 0.5 mg/kg in BALB mice) [103]. This formulation then also confirmed its ability to be effective when administered 3 days a week for 2 weeks in an orthotopic M109-HiFR mouse lung carcinoma model in BALB mice. A significant increase in survival Kaplan Meier curves was observed with the controlled release and sustained retention formulation in comparison to the control group ($p < 0.01$, Log-rank test) whereas CIS powder without TS matrix at its maximum tolerated dose showed no significant increase ($p \geq 0.05$, Log-rank test) [103]. These studies reveal the impact of controlled release and sustained retention of CIS in balancing tolerance and efficacy. Now, this development needs to go further by (i) fine-tuning controlled CIS release to achieve the desired efficacy/toxicity balance and then (ii) evaluating more deeply the anti-tumor efficacy and the systemic and the local tolerance when the formulation is delivered alone or in combination with standard treatments. Scaled-up manufacturing is also ongoing to prepare the first clinical batches.

3.2.2. Nanomedicine-based formulations

Nanomedicine is defined as 'nanotechnology applications in medicine' and includes nanopharmaceuticals, nanoimaging, and theranostics (i.e. combining therapy and imaging) [107]. Nanopharmaceuticals are defined as 'pharmaceuticals engineered on the nanoscale, i.e. pharmaceuticals where the nanomaterial plays the crucial therapeutic role or adds additional functionality to the drug' [108]. Moreover, it can combine multiple agents (e.g. active agent, imaging agent) and carry them together in the same temporal/space dimension by overcoming physicochemical and/or biological barriers, depending on the nanomedicine's pharmacokinetic and biodistribution before the agent(s) are released. Nanomedicine brings new functionalities in comparison with classical formulation strategies due to its nanoscale size. Nanomedicines are usually synthetic constructs that are composed of organic or inorganic matter, the dimensions of at least two axes of which are between 1 and 100(0) nm [109–111]. As with classical formulations, nanomedicine can solubilize a drug, limit drug degradation, control its release, and avoid clearance systems, which modify the drug pharmacokinetic and biodistribution. These new specific functionalities are enhanced drug saturation solubility and therefore dissolution rate, as observed with drug nanocrystals [112]. If they are encapsulated in nanopharmaceuticals, they are able to circumvent physiological barriers or cross barriers (e.g. the blood-brain-barrier [113], the intestinal barrier [114], tumor interstitial fluid [115]). They accumulate drug preferentially and passively into tumors due to the 'enhanced permeability and retention effect' (EPR effect) when administered by the iv route (passive targeting) [116–118]. Moreover, they can selectively and specifically recognize organs, cancer cells, or subcellular compartments (e.g. cytosol) for active targeting [116–118]. Active targeting is usually done by one or more molecular recognition forms (i.e. ligands) attached to the surface of the nanomedicine. These ligands facilitate a drug or drug formulation to interact specifically with a disease-causing molecular phenomenon and/or to recognize and bind to target tissues or cells [107,118]. The ligands are target-specific natural or artificial receptor ligands or target-specific antibodies attached to drugs or drug formulations to target overexpressed receptors [107,116,118]. The receptor on the cell surface can allow its cell internalization (e.g. by receptor-mediated endocytosis and endosomal escape) or an enhanced drug gradient across membranes [107,116,118].

Nanomedicine has led to a number of applications, with ~50 nanopharmaceuticals approved by the FDA and available for use in clinical practice, a fifth of which have oncologic indications [107,110,117,118]. For cancers, most of them have led to a higher therapeutic ratio, mainly by decreasing toxicity [107,117,118]. Nowadays, nanomedicine in oncology is more envisaged as a drug-delivery platform to actively target cancer cells, to be accumulated into lymph nodes, and/or to increase the response to immunotherapy [107].

Immunotherapy has shown spectacular results, with complete cures and inducing long-term survival in advanced-stage patients [111,119]. Unfortunately, immunotherapy only works well in relatively small subsets of patients and can induce significant toxicities [111,119,120]. Therefore, the new hope is that nanomedicine could boost therapeutic outcomes by tuning 'cold' nonimmunoresponsive tumors or metastases into 'hot' immunoresponsive lesions [107,111,118–120]. Three approaches can be used for this purpose: (i) targeting cancer cells to trigger the release of tumor antigens and danger–associated molecular patterns to promote the generation of CD8+ cytotoxic T cells, (ii) targeting the tumor immune microenvironment to inhibit immunosuppressive cells, reduce the expression of immunosuppressive molecules, or promote the activity of antigen-presenting cells and cytotoxic T cells, or (iii) targeting the peripheral immune system to enhance antigen presentation and cytotoxic T cell production in secondary lymphoid organs such as lymph nodes and the spleen, or to engineer and strengthen peripheral effector immune cell population, thereby promoting anticancer immunity [111].

In terms of accumulation in lymph nodes, which are also the first sites of metastases, the functionalities brought by nanomedicine can increase the concentration of drug/active agent preferentially into lymph nodes [110,121–123]. For example, ferumoxytol particles (Feraheme™, AMAG Pharmaceutical), which are iron oxide nanoparticles approved for iron deficiency anemia in adult patients with chronic kidney disease [110], are now being investigated in clinical trials to enhance magnetic resonance lymph node imaging for early staging of lymph node metastasis (completed in 2019, NCT01815333)[**clinicaltrials.gov**].

Currently, promising results seem to be obtained with active-targeted nanomedicines, which are included in the next-generation drugs in clinical trials using nanopharmaceuticals [107]. For example, denileukin diftitox (Ontak®, Eisai Medical Research) was the first actively targeted proteinaceous nanoparticle and was approved in 2008. It combines an

engineered fusion protein that combines targeting proteins with cytotoxic molecules (i.e. IL-2 receptor antagonist coupled to diphtheria toxin to target cells that overexpress the IL-2 receptor on T cells to combat an aggressive form of non-Hogkin's peripheral T-cell lymphomas) [107].

However, there are high barriers when active-targeted nanomedicines as well as other nanomedicines are delivered by iv. The EPR effect seemed to be the 'royal road' to passively accumulate nanomedicine into a tumor. Despite the promising results first observed in preclinical studies, this effect has turned out to be quite limited in clinical trials as it varies between both patients and tumor types, and even within the same patient or tumor type over time [116,118,124]. The extravasation from blood vessels in the tumor interstitium is a nonspecific process that is the rate-limiting factor of nanocarrier localization [116,117,124]. Moreover, solid tumors are difficult for the nanocarrier to penetrate and diffuse into [116,117,124]. Size, shape, and surface chemistry have been identified as the major characteristics responsible for nanomedicine diffusion inside the tumor mass [115–117,124]. Therefore, many nonspecific factors (e.g. protein corona, drug circulation time, tumor vascular permeability, tumor interstitial fluid pressure) may mask the contribution of the specific targeting to the nanocarrier accumulation into the tumor [116,118]. Moreover, the actively-targeted nanocarriers also have to pass through numerous additional barriers, such as multiple cell layers, before binding to the targeted cancer cells [116–118]. All these barriers can hide the contribution of the active-targeting.

One evident approach to largely overcoming these issues should be the delivery of the actively targeted nanocarriers directly into the tumor site and therefore by inhalation for lung tumors [116,117]. Nanomedicine by inhalation brings new hope of adding functionalities to the drug to act on cancer cells in tumors [117,118], tumor microenvironments [117,118], or metastases [110], and to diffuse in the lymph nodes [125] (Figures 1 and 2).

Inhaled nanomedicines are usually developed as liquid dispersions (i.e. adapted to nebulizers) and are widely described in reviews [77,88,126] and book chapters [127]. Interesting preclinical developments have shown that an epidermal growth factor (EGF) ligand grafted onto the surface of gelatine nanoparticles (i.e. active targeting) has induced a higher accumulation of nanoparticles (than non-targeted nanoparticles) in A549 lung tumors of a murine model that overexpresses EGF receptor [128,129]. Moreover, the EGF-targeted nanoparticles accumulated at a 3.6 times higher concentration from 30 min until 24 h after aerosol administration in the A549 tumor-grafted mouse lungs compared to in healthy mouse lungs, confirming the effective targeting of the tumor tissues *in vivo* [128,129]. Another interesting study in active targeting by inhalation is on the use of a modified synthetic analogue of luteinizing hormone-releasing hormone (LHRH) grafted onto the surface of nanostructured lipid carriers that have shown a selective accumulation in lung tumors *in vivo*, avoiding healthy lung tissue when compared to non-LHRH-targeted labeled nanostructured lipid carriers [130]. In terms of the therapeutic response, targeted nanostructured lipid carriers loaded with paclitaxel and siRNA (to silence proteins related to efflux and antiapoptotic defense mechanisms, i.e. MRP1 and BCL2 proteins, respectively) led to improved antitumor activity compared to an iv conventional solvent-based paclitaxel formulation (i.e. an about 40-fold decrease in tumor volume), allowing regression in 50% of mice [130].

Cytotoxic-based nanomedicine (as liposomes to solubilize, stabilize, and sustain the drug release) has been already tested in phase I and phase Ib/IIa by nebulization using 9NC or cisplatin [34–36] (Table 1). However, no clinical trials have been made by inhalation using active-targeting nanomedicine and/or as a dry powder until now.

However, if nanomedicines are formulated as dry powders, that will require specific pharmaceutical developments. The nanomedicine will need to be formulated as nano-in-microparticles (or nano-embedded microparticles) or reversible nanoparticle agglomerates that are able to be inhaled (Dae between 1 and 5 µm) and then re-dispersed to generate individualized nanoparticles since they are in contact with the lung fluids [57,126,127,131]. This approach often requires additional excipients in the formulation, which dilute the final drug content and can induce additional tolerance concerns. Moreover, it also involves additional production steps that can complicate the pharmaceutical development [127]. All these aspects are important and currently limit the development of this promising pharmaceutical strategy in lung cancer therapy.

To illustrate this last point, there have been pharmaceutical developments to develop dry powders based on folate grafted-solid lipid nanoparticles (SLNs) [132] or folate-grafted-micelles [133] that encapsulated paclitaxel to target the folate receptor, of which the α-form is overexpressed in lung cancer (i.e. 60% of NSCLC and mainly in adenocarcinoma [134]). These folate-grafted SLNs and micelles have shown an increased antiproliferative activity *in vitro* and a penetration into folate receptor-lung cancer cells *in vitro* and into lung tumor *in vivo* [132,133]. Due to their sustained-release properties (10% of paclitaxel released each 24 h *in vitro*), folate-grafted SLNs have prolonged pulmonary exposure to paclitaxel to up to 6 h following pulmonary delivery in healthy mice [132]. The folate-grafted SLNs were in a DPI formulation, using spray-drying techniques and appropriate excipients (i.e. dextran, recognized as GRAS [57]). This resulted in good aerodynamic properties, with FPF of up to 34% and an ability of the initial nanocarriers to re-disperse in physiological buffer [132]. The main limitation of these DPI formulations was the drug loading, which was up to 0.46 w/w (i.e. 4.6% of paclitaxel loading in folate-grafted SLNs diluted in a dextran matrix at a ratio of 10:90 w/w). This loading was not sufficient to deliver effective paclitaxel doses within a reasonable time to patients. Therefore, folate grafted-nanocrystals embedded in DPI formulations with mannitol, which is an excipient authorized for inhalation, were developed [132]. The nanocrystals coated with the folate-PEG-HTCC copolymer at 40% w/w allowed the paclitaxel release to be slowed down (i.e. to 25% after 8 h in comparison with 100% after 8 h for uncoated paclitaxel nanocrystals). That increased paclitaxel loading up to 2% and the FPF to 45% of the dry powder. However, even though the drug loading in folate-based nanocrystals increased by 12 times (i.e. 55% vs 4.6% w/w), they needed a higher amount

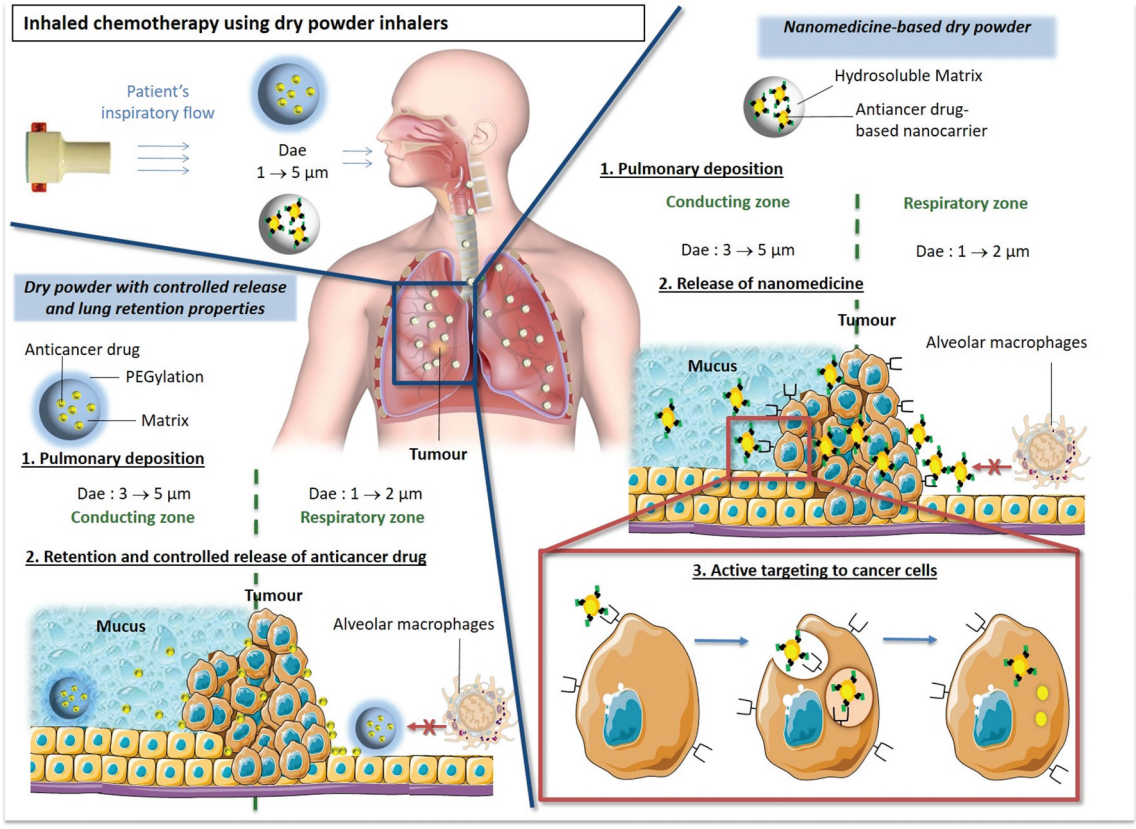

Figure 2. Dry powder for inhalation based on (i) microparticles with controlled drug release and with increased lung retention properties, or (ii) nanomedicines – Deposition and fate in tumor-bearing lung. (1) Inhaled particles will deposit according to their aerodynamic diameter (Dae) in the conducting zone (Dae between 3 and 5 µm) or the respiratory zone (Dae between 1 and 2 µm). (2) After dispersion in lung fluids, particles will progressively release the drug and will escape the non-absorptive clearance systems due to their composition, surface properties, and/or size. (3) The use of nanomedicine allows active targeting of cancer cells with intracellular delivery of the anticancer drug by recognition of a ligand on the nanomedicine surface by an endocytosis-mediated receptor. Adapted from Rosière *et al* [24]

of excipient in the matrix (i.e. 96% vs 90%) to fully re-disperse the coated nanocrystals. Nevertheless, these formulations led to 6-fold increases in the fine particle dose for SLN-based DPI. This improvement allows this formulation to be considered for further development, i.e. efficacy and safety studies in animal models.

Despite the hope and possibilities that nanomedicine can bring to drug/active agents, nanomedicine faces several major challenges that limit its translation to the clinic and the market [117,118,135]. For instance, one technological challenge is to obtain a suitable drug payload in nanopharmaceuticals, which is often in the range of 1–10% w/w. In addition to the inability of these nanopharmaceuticals to deliver sufficient drug doses, the amount of excipient in the nanopharmaceutical is therefore too great and could accumulate, leading to adverse effects [135]. Moreover, the interactions of nanopharmaceuticals with the biological environment are difficult to evaluate and anticipate as these technologies present a huge specific surface that can form agglomerates or aggregates of nanopharmaceuticals in complex media, which can behave completely different to the initial nanopharmaceutical. That leads to a controversial debate about their safety. With regards to the authorities, the applicability for nanomedicines is also limited due to the need for better characterization, possible toxicity issues, a lack of specific regulatory guidelines, cost-benefit considerations, and waning enthusiasm among some healthcare professionals [107].

Moreover, production of large nanopharmaceutical batches as well as a lack of robust reproducibility of nanopharmaceutical characteristics (i.e. drug loading, particle size distribution, shape/structure, surface chemistry, stability, drug release) might also be responsible for the poor transfer of nanomedicine to clinical practice [117,126,135]. Moreover, the more complex the system, the more difficult it is to produce and to characterize.

4. New positions in the standard of care to overcome the clinical challenges

4.1. Changes in the standard of care

Tumors in the lower respiratory tract are a major public health problem worldwide. On the one hand, primary lung cancers (NSCLC and SCLC) are among the most frequent forms, with 2.09 million cases in 2018, and the most deadliest, with 1.76 million deaths in 2018 worldwide [136]. On the other hand, the lung is one of the most frequent sites of metastasis from primary cancers: lung, colorectal, breast, prostate, bladder, head and neck, bone, osteosarcoma, soft tissue sarcoma,

melanoma, thyroid, and testicular cancers [3–5]. The prognosis is usually low, with a 5-year survival rate of 20.5% for all stages of primary lung cancers (in the USA between 2010 and 2016), and, 5–80% for pulmonary metastasis, depending on the primary cancer [3,137]. This low prognosis for primary lung cancers is due to late diagnosis in patients, who present a relatively advanced stage (i.e. 22% in the regional stage and 57% in the distant stage) [137]. This late diagnosis is explained by a lack of symptoms and by there being no screening campaign in high-risk populations. Promising benefits could be obtained using low-dose chest computed tomography as a screening technique for early detection in a high-risk population, but this has not yet been applied [1]. Regional recurrence is also a prominent issue for survivors, with up to 45% and 55% experiencing stage I and II NSCLC and up to 65% experiencing limited-disease SCLC due to loco-regional lymph node involvement [138,139].

The treatment of lung cancer depends on the stage of the disease, tumor histology, the presence of biomarkers, and on patients' comorbidities. The current therapeutic modalities for NSCLC are surgery and radiotherapy as localized treatments and cytotoxic chemotherapy (e.g. platinum doublets including a third-generation drug [29]), targeted therapy, and immunotherapy (i.e. immune checkpoint inhibitors (ICIs)) as systemic treatments [140,141]. In the last decade, significant advances in therapies for metastatic lung cancers have been observed. First, a better knowledge of targeted therapies and their position in stage IV NSCLC have permitted an increase in the 5-year survival rate (for NSCLC, from 16% (1999–2006) to up to 19.4% (2009–2015)), considering that the stage distribution has remained relatively stable this last decade [137,142]. However, targeted therapies are the current standard of care for limited subpopulations of stage IV NSCLC patients (i.e. 10% with EGFR mutations, 5% with ALK translocation, 1–2% with ROS1 translocation) [1,141]. Second, following very good results in phase III, ICIs have led to deep adaptations in the landscape of therapeutic approaches for advanced-stage patients [143,144]. They are used as first and second lines in unresected stage III and stage IV NSCLC [144], and extensive-stage SCLC [145], and are currently being investigated for resected NSCLC [146,147]. The most widely used in lung cancer is the anti-PD1 pembrolizumab (first approval received for NSCLC by the FDA in 2015), which is now the standard of care for stage IV NSCLC patients with no driver mutations, i.e. when no targeted therapy is indicated [144]. The current recommendations for its clinical use are currently driven by the programmed-death ligand-1 protein (PD-L1) tumor proportion score (TPS). It is recommended as monotherapy for stage IV NSCLC patients with a PD-L1 TPS of more than 50% (i.e. ~30% of stage IV NSCLC patients) or combined to a standard platinum doublet chemotherapy (PD-L1 TPS below 50%, which represents ~60% of stage IV NSCLC patients) [148,149]. This combination approach highlights the role of cytotoxic chemotherapy, which remains essential in the care of the majority of patients with lung tumors [150,151]. Cytotoxic chemotherapy remains a reality for most advanced-stage SCLC and NSCLC patients, except those for whom a targeted therapy (~15% stage IV NSCLC patients) or a pembrolizumab monotherapy (~30% stage IV NSCLC) is indicated.

4.2. Position of inhaled cytotoxic chemotherapy in the standard of care

Inhaled cytotoxic chemotherapy could be part of the conventional treatment of lung cancer in many ways, considering that systemic chemotherapy plays a pivotal role in the care of lung cancer patients [150,151]. However, subpopulations of patients who will potentially benefit from inhaled cytotoxic chemotherapy must be identified according to tumor localization and size, clinical stage, cancer histology, and the cytotoxic drug as well as the patient's lung capacity and function and therefore subjacent respiratory diseases [77]. The position of inhaled cytotoxic chemotherapy is here discussed regarding the potential benefit/risk ratio of this approach. The approach has been built on (i) preclinical and mainly clinical reports, (ii) opportunities related to the inhalation technologies available today or in near future, and (iii) recent progress in knowledge of lung cancer biology and its therapies.

The first main indications of inhaled cytotoxic chemotherapy in lung cancer could be in combination with ICIs in various patient populations. Due to their cytotoxic properties (e.g. DNA damaging), certain anticancer drugs have been able to induce various immune effects such as increasing neoantigen repertoire and antigen presentation, inducing immunogenic cell death, promoting proinflammatory cytokine release, down-regulating regulatory immune cells, or affecting programmed cell death 1 protein (PD1)/PD-L1 expression [152]. These immune effects could explained, at least partly, by the good results observed in lung cancer patients of the ICI and systemic chemotherapy combination [151,153,154]. Inhaled cytotoxic chemotherapy could expand these antitumor immune effects because it could (i) induce local cytotoxic activity (i.e. in the primary lung tumor and potentially in the lung lymph nodes [22]), (ii) with high frequency (iii) and without interruptions, (iv) while maintaining low systemic exposure and consequently low immunosuppressive toxicities [39,40]. Similarities can be found in the concept of metronomic chemotherapy, which relates to the use of chemotherapy at subtoxic systemic doses administered continuously at high frequency, i.e. two to three administrations a week [155]. This concept has recently been reintroduced in clinical research, partly due to understanding of the involvement of the immune system and possible combinations with immunotherapy [155–157].

Combinations of inhaled cytotoxic chemotherapy with ICIs could first be considered in advanced-stage patients with regard to the current used of ICIs in unresectable-stage III and stage IV NSCLC [144] and extensive-stage SCLC [145]. In the current ICI-based standards of care for advanced-stage lung cancers, two main indications can be envisaged. For patients for whom a pembrolizumab monotherapy is indicated (i.e. with a PD-L1 TPS higher or equal to 50%), inhaled cytotoxic chemotherapy could be suggested as an add-on treatment, with a potentially better immunogenic antitumor response without a significant increase in the systemic

toxicities. However, attention should be paid to lung toxicity, which is one of the most reported fatal toxic effects of ICIs [158]. For patients for whom an ICI and a systemic chemotherapy are indicated (i.e. PD-L1 TPS below 50%), inhaled cytotoxic chemotherapy could be positioned as either an add-on treatment or as an alternative to (part of) the dose of systemic chemotherapy. In the case of an add-on therapy, the potential increase in systemic toxicities could be investigated in depth, in particular, if the cytotoxic drug is delivered through both the pulmonary and the iv routes. As advanced-stage lung cancers are systemic diseases, the observation of a systemic or 'abscopal' response, as observed with radiotherapy in metastatic NSCLC patients in phase 2 recently [151], would be important. Following the same approach, inhaled cytotoxic chemotherapy/ICIs combinations could also be considered in early stages, depending on the outcomes of the ongoing trials of neoadjuvant and adjuvant ICIs in resected early-stage NSCLC [146,147].

Another possible position of inhaled cytotoxic chemotherapy in lung cancer treatment is as an alternative to systemic chemotherapy, mainly in resected early-stage NSCLC as a neoadjuvant or adjuvant to surgery [77]. In this approach, a substitution of a part or the entire systemic dose with an inhaled dose of cytotoxic drugs that induce relatively severe systemic toxicity (e.g. platinum derivatives) can be envisaged [40,77].

Lastly, treatment of pulmonary metastases of other cancers that spread preferentially to the lungs, e.g. osteosarcoma, is a promising indication for inhaled cytotoxic chemotherapy, in curative but also in preventive care [36,77].

Regarding the specific advantageous and limitations of inhaled cytotoxic chemotherapy and its potential implementation in the care of lung cancer patients, the key to success seems to be linked to the ability to treat the lung tumor with a high frequency. Two main characteristics enable high frequency of administration: (i) an advantageous biodistribution of cytotoxic drug with lung targeting and limited systemic exposure, and (ii) practical benefits to patients, ensuring a good compliance with treatment. Although advantageous biodistribution can be theoretically observed regardless of the inhalation technology, high frequency of administration can only be put in place with tailored technologies and devices. In practice, patient visits to the hospital several days a week cannot be considered. Therefore, to benefit from the therapeutic potential of inhaled cytotoxic chemotherapy, administration should be considered at home with appropriate inhalation technology. Containment of chemotherapy during administration (dose preparation, aerosolization, inhalation, and exhalation) is therefore key and could be possible with tailored DPIs. As a similar concept, it must be noted that the concept of metronomic chemotherapy has been mainly developed with drugs available for oral delivery [159].

5. Conclusion

Inhaled cytotoxic chemotherapy is a promising therapeutic modality that can fill the gap between the localized and the systemic treatments in lung cancers. However, technological and clinical challenges have been identified during clinical trials and have limited its applicability and pharmaceutical development. Therefore, no product has reached the market yet. Nowadays, novel developments in the field and changes in clinical practice for patients with advanced diseases bring new hopes and opportunities. DPIs that could be tailored as a disposable device seem to be a more appropriate inhalation device for inhaled cytotoxic chemotherapy in comparison with nebulizers. Their main advantage is that they present an administration generated by the patient's inspiratory airflow, which limits the air contamination and takes little time. Moreover, dry powder formulations can be more appropriate for poorly-water soluble cytotoxic drugs and could be designed to optimize their efficacy and lung tolerance. Controlled release and sustained retention strategies with low amounts of excipients are the most promising in terms of translation from clinical studies to the market. Moreover, the advent of immunotherapy in patients with advanced diseases brings new opportunities for inhaled cytotoxic chemotherapy to reveal its added value compared with standard treatments.

6. Expert opinion

Lung cancers and lung metastases present a very high incidence and are the leading cause of cancer mortality. The current treatment modalities for the most frequent primary cancer, NSCLC, combine localized treatment (i.e. surgery and radiotherapy) and systemic treatments (i.e. cytotoxic chemotherapy, targeted therapy, and immunotherapy) according to the stage of the disease, which is mostly advanced. Until now, these curative but mostly palliative treatments have achieved some progress. Their 5-year survival rate is about 20%, which remains low and shows that there is still a need for early detection and additional or improved therapies. Early detection through a screening campaign in high-risk populations could change the stage distribution, with more localized and regional-stage disease and lower advanced-stage disease, which would present a better prognosis.

Inhaled cytotoxic chemotherapy is a promising therapy to fill the gap between the localized and the diffuse systemic treatments as a loco-regional treatment. It would concentrate the dose into the lungs and diffuse it progressively into the blood and lymph system, which are the main routes of cancer invasion. Nebulizers have been the first type of device used to evaluate this concept. Although nebulizers presented technological issues (i.e. a huge administration time due to low drug concentrations in the nebulizer formulation, and air/device contamination, which requires cumbersome healthcare protection) and clinical concerns (i.e. clinical trials made on advanced patients sometimes previously treated with cytotoxic chemotherapy, and anticancer drugs presenting pulmonary toxicity and/or a rapid clearance). These technological and clinical issues have limited the proof of concept and the development of this promising therapy. Therefore, we propose to use disposable DPI with potential contained contamination as a new device for inhaled cytotoxic chemotherapy to overcome the technological issues. A formulation strategy needs

to be developed to balance the anti-tumor efficacy and the lung tolerance to overcome the clinical concerns. For that, dry powders based on controlled drug release and with sustained lung retention are quite promising. However, they will need to present a high drug loading and an FPF able to be deposited into the lung as well as scalable production techniques with an acceptable yield and using excipients acceptable for or highly biocompatible with inhalation. Until now, more classical formulations have seemed more appropriate to reaching these objectives than nanomedicine. In fact, nanomedicine, despite its possible additional functionality to target cancer or immune cells or the tumor microenvironment and lymph nodes, has shown obstacles to their clinical translation. These obstacles are poor drug loading and poorly scalable production techniques as well as characterization that is insufficiently defined to be easily approved by authorities. However, progress has been made over thirty years and a lot of knowledge about nanomedicines has been revealed.

In the clinics, the advent of immunotherapy, in particular with ICIs, has changed drastically the standard of care for advanced NSCLC patients, and new opportunities are emerging. In this context, inhaled cytotoxic chemotherapy could prove its potential by using dry powder for inhalation design to improve the response of patients to immunotherapy with or without systemic cytotoxic chemotherapy. After this first step, inhaled chemotherapy could be evaluated as an add-on treatment with systemic cytotoxic chemotherapy as well as with localized treatment such as surgery on regional and localized stages to evaluate its impact on micrometastases and lung recurrences.

Funding

This paper was funded by the Unit of Pharmaceutics and Biopharmaceutics.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Declaration of interest

K. Amighi, N. Wauthoz, and R. Rosière are inventors of patents related to some technologies described in the review and are co-founders of Inhatarget Therapeutics. R. Rosière is also the CSO of Inhatarget Therapeutics and a scientific collaborator of the Unit of Pharmaceutics and Biopharmaceutics. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

List of abbreviations

5-FU:5-fluorouracil
9-NC: 9-nitrocamptothecin
AUC: area under the curve
CIS: cisplatin
COPD: chronic obstructive pulmonary disease
Dae: aerodynamic diameter
DPI: dry powder inhaler
DLT: dose-limiting toxicity
EGF: epidermal growth factor
EPR: enhanced permeability and retention
FPF: fine particle fraction
GRAS: generally recognized as safe
ICI: immune checkpoint inhibitor
iv: intravenous
LHRH: luteinizing hormone-releasing hormone
NCT: clinicaltrials.gov identifier
NSCLC: non-small cell lung cancer
PD1: programmed cell death 1 protein
PD-L1: programmed-death ligand-1 protein
SCLC: small cell lung cancer
siRNA: small interfering ribonucleic acid
SLN: solid lipid nanoparticle
TPS: tumor proportion score
TS: tristearin
TPGS: tocopheryl PEG1000 succinate

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