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Recommended Citation

Hohenforst-Schmidt W, Zarogoulidis P, Pitsiou G, Linsmeier B, Tsavlis D, Kioumis I, Papadaki E, Freitag L, Tsiouda T, Turner JF, Browning R, Simoff M, Sachpekidis N, Tsakiridis K, Zaric B, Yarmus L, Baka S, Stratakos G, and Rittger H. Drug eluting stents for malignant airway obstruction: A critical review of the literature J Cancer 2016; 7(4):377-390.

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Review

Drug Eluting Stents for Malignant Airway Obstruction: A Critical Review of the Literature

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Received: 2015.08.20; Accepted: 2015.11.01; Published: 2016.01.13

Abstract

Lung cancer being the most prevalent malignancy in men and the 3rd most frequent in women is still associated with dismal prognosis due to advanced disease at the time of diagnosis. Novel targeted therapies are already on the market and several others are under investigation. However non-specific cytotoxic agents still remain the cornerstone of treatment for many patients. Central airways stenosis or obstruction may often complicate and decrease quality of life and survival of these patients. Interventional pulmonology modalities (mainly debulking and stent placement) can alleviate symptoms related to airways stenosis and improve the quality of life of patients. Mitomycin C and sirolimus have been observed to assist a successful stent placement by reducing granuloma tissue formation. Additionally, these drugs enhance the normal tissue ability against cancer cell infiltration. In this mini review we will concentrate on mitomycin C and sirolimus and their use in stent placement.

Key words: pharmacology, stents.

Introduction

Lung cancer still remains a difficult to treat cancer, since patients are diagnosed at late stage disease due to lack of symptoms.[1] Moreover; lung cancer is the second most lethal cancer after prostate for men and breast for women, with a trend to increase for women in the future.[1] Several medical societies are trying to identify those groups of patients that will benefit from imaging screening with several novel

techniques.[2-4] Until now there is no algorithm for early diagnostic approach for lung cancer, and patients are usually investigated if symptoms appear. In the last decade several molecular pathways have been investigated and several novel drugs are already on the market for non-small cell lung cancer (NSCLC).[5-8] Regarding small cell lung cancer (SCLC) we still do not have novel therapies, however;

novel treatment approaches are investigated with the main concept of immunomodulation being the most feasible right now.[9-14] Side effects from non-specific cytotoxic agents are well known and there are several patients that have to postpone their treatment.[15, 16] Apart from the side effects induced by the chemotherapeutic agents, there are several situations where the tumor has infiltrated different parts of the airways and respiratory distress is observed.[17] Several techniques can be used to open a closed central airway and chemotherapy or radiotherapy can be used to preserve the result.[18, 19] Debulking of cancer tissue is usually performed with different types of lasers, electrocautery, argon plasma coagulation (APC) or cryotherapy.[20] (Figures 1-2) In order to keep the airway opened we use additionally stent devices.[20, 21] Ballon dilatation and photodynamic therapy (PDT) are other options with specific indications [22, 23] There is also a classification system for airway stenosis that can be used by medical practitioners.[24] Stents have been used for tracheal and esophageal fistulas.[25, 26] For malignant airway stenosis we usually use self-expanding covered or uncovered stents. [21] In order to keep the good result of debulking cancer tissue we have to choose carefully the right time of debulking with systemic, intratumoral [27,149] (or a combination of both modalities of) chemotherapy and / or radiotherapy. Moreover; it has been observed that different stents (diameter, length, materials) induce different local stress.[28] Furthermore stents induce locally stress to the sur-

rounding tissues. They increase proliferation of granuloma tissue in benign airway stenosis and increase angiogenesis. Cancer tissue which already has increased angiogenesis when more stress is applied locally shows further enhanced tissue formation.[29] Therefore novel cytokine eluting stents are being developed.[30] Furthermore, novel research of stent placement at least for the gastrointestinal tract has indicated that stent placement might induce cancer cell migration.[31] Several drugs have been used as adjuvant local application in order to preserve the airway passage.[30, 32-36] In this review we will focus on the drugs that have been used with stents, their pharmacological activity and future applications. Additionally, we will include studies with data applicable for lung cancer patients.

Search strategy

We performed an electronic article search through PubMed, Google Scholar, Medscape and Scopus databases, using combinations of the following keywords: mitomycin c, floxuridine, sirolimus, stents, lung cancer stents, dumon stents, zotarolimus, rapamycin, 5-fluorouracil, doxycycline, everolimus and pirfenidone. All types of articles (randomised controlled trials, clinical observational cohort studies, review articles, case reports) were included. Selected references from identified articles were searched for further consideration.

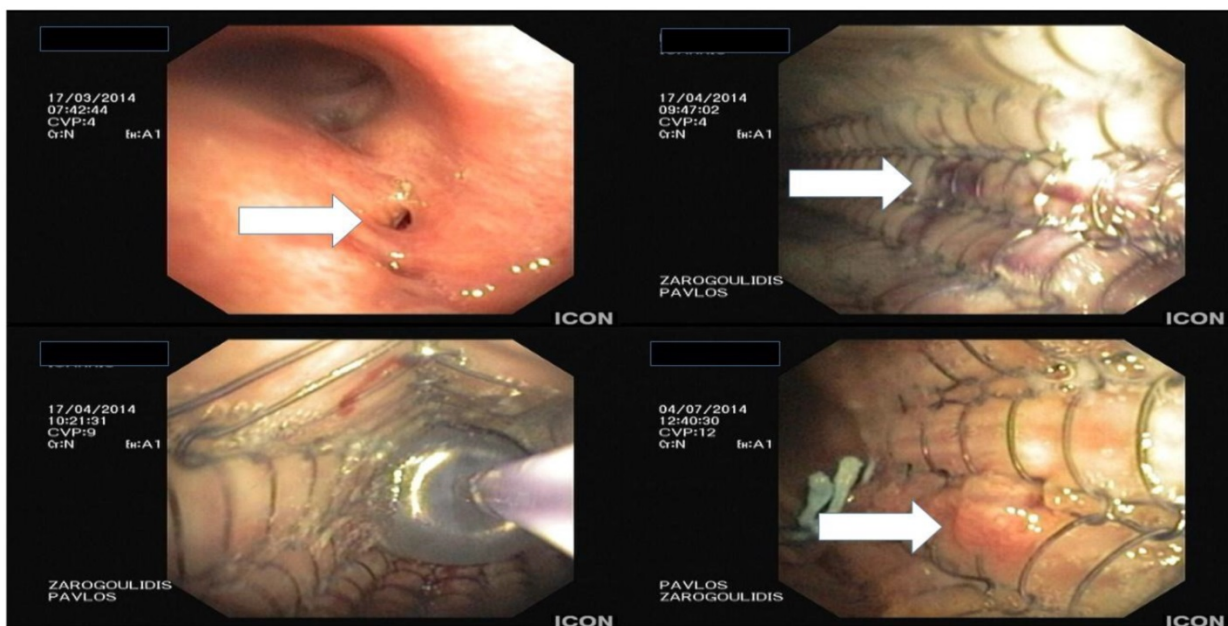


Figure 1. From top left to right bottom, hole made from excision of paratracheal tumor and covered stent placement with balloon dilatation.

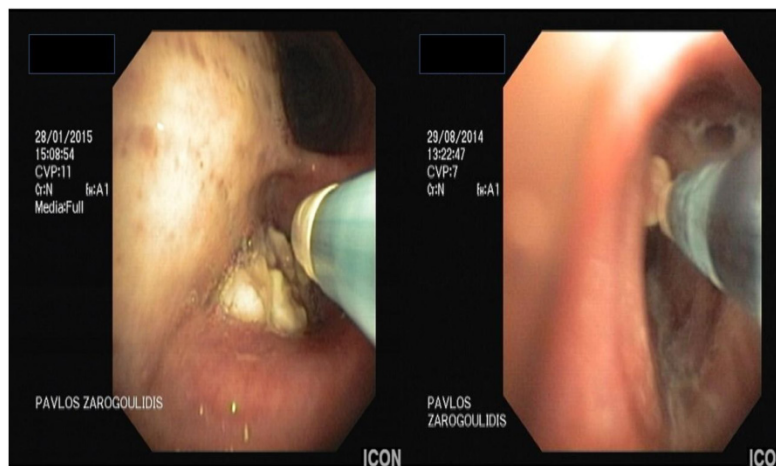


Figure 2. Argon plasma debulking.

Drug Pharmacology

Cisplatin

Cisplatin, is a well-known non-specific chemotherapy drug. It is one of the first member of a class of platinum-containing anti-cancer drugs. These days this group of drugs includes carboplatin, oxaliplatin and lipoplatin. These platinum complexes react *in vivo*, binding to and causing crosslinking of DNA, which finally induce apoptosis. Cisplatin is usually administered intravenously as short-term infusion in normal saline for treatment. It is used to treat (non-)small cell lung cancer, ovarian cancer, lymphomas, bladder cancer, cervical cancer, and germ cell tumors.[37] Cisplatin has been observed to be particularly effective against testicular cancer; the cure rate was improved from 10% to 85%.[38]

Cisplatin is known to crosslink DNA in several different ways, interfering with cell division by mitosis. The damaged DNA elicits DNA repair mechanisms, which in turn activate apoptosis. Most notable among the changes in DNA are the 1,2-intrastrand cross-links with purine bases. These include 1,2-intrastrand d(GpG) adducts which form nearly 90% of the adducts and the less common 1,2-intrastrand d(ApG) adducts. 1,3-intrastrand d(GpXpG) adducts occur but are readily excised by the nucleotide excision repair (NER). Cisplatin has no alkyl group unable to carry out alkylating reactions. However; it is correctly classified as alkylating-like.[39, 40] Of note is the fact that different chemotherapeutic especially alkylating agents (like cyclophosphamide) play a specific role as causative for initiation / aggravation of (underlying) pulmonary hypertension in cancer patients during specific cancer treatment.[27] Such a (by chemotherapy) induced pulmonary hypertension is often classified as pulmonary veno-occlusive disease (PVOD) which

resembles in many features a typical pulmonary arterial hypertension but is accompanied with a much worse prognosis in comparison to e.g. an idiopathic pulmonary arterial hypertension. Furthermore the diagnosis of induced PVOD is even more difficult when other hemodynamic comorbidities like left heart disease is already existing on chemotherapy initiation. It is worth mentioning that the establishment of the diagnosis of PVOD itself is very difficult and many times only possible post-mortal. In regards to real-life scenarios with underlying hemodynamic relevant comorbidities it is one of the most complex diagnosis in medicine in human beings alive. Therefore we believe that this diagnosis may be underscored in cancer patients and could be a part of the explanation for the still worse prognosis in many solid cancers especially under treatment despite new, very expensive targeted therapies. It has to be mentioned that any reduction of cardiac output will increase the interstitial fluid pressure intratumorally which is linked to a worse efficacy of any cancer treatment.

Cisplatin resistance

Cisplatin combination chemotherapy is the cornerstone treatment of many cancers. However; many cancer patients will eventually relapse with cisplatin-resistant disease. Mechanisms regarding the cisplatin resistance have been proposed including changes in cellular uptake and efflux of the drug, increased detoxification of the drug, inhibition of apoptosis and increased DNA repair.[41, 42] Oxaliplatin is active in highly cisplatin-resistant cancer cells in the laboratory but there is little evidence for its activity in the clinical treatment of patients with cisplatin-resistant cancer. The drug paclitaxel may be useful in the treatment of cisplatin-resistant cancer; the mechanism for this activity is yet unknown.[43] In regards to hemodynamic properties of paclitaxel it is

of interest that this drug can influence the altitude of life limiting pulmonary hypertension positively via the Forkhead box O (FoxO) transcription factors which are key regulators of cellular proliferation. Using intravenous or inhaled paclitaxel will lead to pharmacological reconstitution of FoxO1 transcription factor activity in pulmonary artery smooth muscle cells (PASMCs) which serves as a potential treatment option for pulmonary hypertension.[44] This detail may be of interest when discussing chemotherapy options in cancer patients with severe pulmonary hypertension beside cancer diagnosis especially in the situation of no or minor response to first line cisplatin.

Fluorouracil

Fluorouracil is a pyrimidine analog drug which is used in the treatment of cancer. It is a suicide inhibitor and works through irreversible inhibition of thymidylate synthase. This drug is an antimetabolite. 5-Fluorouracil acts primarily as a thymidylate synthase (TS) inhibitor. Its main action is to block the synthesis of the pyrimidine thymidine which is a nucleoside required for DNA replication. Thymidylate synthase methylates deoxyuridine monophosphate (dUMP) in order to synthesize thymidine monophosphate (dTMP). The administration of 5-FU induces cell death via thymineless death.[45] Calcium folinate stabilises the 5-FU-TS complex and enhances 5-FU's cytotoxicity.[46] There is very little difference between the minimum effective dose and maximum tolerated dose of 5-FU, and it has been observed that the drug exhibits individual pharmacokinetic variability.[47-49] Therefore, an identical dose of 5-FU may result in different therapeutic response between patients.[48] It has been observed that both overdosing and underdosing are of concern with 5-FU. Moreover; the majority of colorectal cancer patients treated with 5-FU are underdosed based on today's dosing standard, body surface area (BSA).[50-53] The limitations of BSA-based dosing is an issue for many physicians as they cannot accurately titer the dosage of 5-FU for the majority of individual patients, which results in sub-optimal treatment efficacy or excessive toxicity.[51, 52]

The dihydropyrimidine dehydrogenase (DPD) enzyme is responsible for the detoxifying metabolism of fluoropyrimidines, a class of drugs that includes 5-fluorouracil, tegafur and capecitabine[54] Moreover; genetic variations within the DPD gene (*DPYD*) can lead to reduced or absent dihydropyrimidine dehydrogenase activity, and individuals who are heterozygous or homozygous for these variations may have partial or complete DPD deficiency. It is estimated that about 0.2% of individuals have complete dihy-

dropyrimidine dehydrogenase deficiency.[54, 55] Those patients with partial or complete dihydropyrimidine dehydrogenase deficiency have increased risk of severe or even fatal drug toxicities when treated with fluoropyrimidines; such as; neurotoxicity, myelosuppression.[55, 56]

At least two studies have found significant relationships between concentrations of 5-FU in blood plasma and both desirable or undesirable effects on patients. [52, 56] Further evaluation of the drug is based on the concentration of 5-FU in plasma that can increase desirable outcomes while minimizing negative side effects of 5-FU therapy.[52, 56] Towards this direction a blood test has been created and is being used in some centers as My5-FU test.[53]

Floxuridine

Floxuridine is an antimetabolite. The drug is mostly used in the treatment of colorectal cancer. Floxuridine, an analog of 5-fluorouracil, is a fluorinated pyrimidine.

Mitomycin C

The mitomycins are a family of aziridine-containing natural products isolated from *Streptomyces caespitosus* or *Streptomyces lavendulae*. Mitomycin C (MTC, an antibiotic), finds use as a chemotherapeutic agent by virtue of its antitumour activity. It is applied intravenously to treat upper gastro-intestinal cancers (e.g. esophageal carcinoma), breast cancers and anal cancers, moreover; in bladder instillation for superficial bladder tumours. It causes delayed bone marrow toxicity and therefore it is usually administered at 6-weekly intervals. Prolonged use may result in permanent bone-marrow damage. The usual adverse effects are lung fibrosis and renal damage. Mitomycin C has also been used topically rather than intravenously in several areas, like superficial cancers, particularly bladder cancers and intraperitoneal tumours. It is now well known that a single instillation of this agent within 6 hours on bladder tumor resection can prevent recurrence. Mitomycin C is a potent DNA crosslinker. A single crosslink per genome has shown to be effective in killing bacteria. This is accomplished by reductive activation followed by two N-alkylations. Both alkylations are sequence specific for a guanine nucleoside in the sequence 5'-CpG-3'. [57] Potential bis-alkylating heterocyclic quinones were synthesised in order to explore their antitumoral activities by bioreductive alkylation.[58] Mitomycin is also used as a chemotherapeutic agent in glaucoma surgery.[59] In the study by Li Y. et al. [60] a novel combination of PEGylated phytosomes with mitomycin C has been constructed in order to enhance the efficacy of mitomycin C. PEG complex

has been observed in other studies that induces a "stealth" activity for several chemotherapeutic substances and in this way it produces a release effect for many cytotoxic drugs.[61, 62] In the study by Moiseyenko VM. Et al. [63] it was observed that heavily pretreated ovarian cancer patients carrying germ-line BRCA1 mutation benefited from the administration of mitomycin C. This study provides evidence that several molecular pathways of NSCLC should be investigated along with the local administration of mitomycin C (MTC). In regards to hemodynamic properties of this drug (especially in comparison to the above mentioned details for cisplatin and paclitaxel) it is of interest that MTC intravenous therapy is a potent inducer of PVOD in humans and for intraperitoneal MTC therapy in rats.[64] Amifostine prevents MTC-induced PVOD in rats and should be tested as a preventive therapy for MTC-induced PVOD in humans.

Special Reference to

Pirfenidone

Pirfenidone is an anti-fibrotic drug which is currently used in the treatment of idiopathic pulmonary fibrosis (IPF). It is known to reduce lung fibrosis through downregulation of the production of growth factors and procollagens I and II. Several studies have established its antifibrotic and anti-inflammatory properties in vitro systems and animal models of fibrosis.[65] A number of cell-based studies have shown that pirfenidone reduces fibroblast proliferation,[66-69] inhibits tumor Growth Factor- β (TNF- β) stimulated collagen production[70] and reduces the production of fibrogenic mediators such as TGF- β . [68] The drug has also shown to reduce production of inflammatory mediators such as tumor growth factor- α (TNF- α) and interleukin 1 β (IL-1 β) in both cultured cells and isolated human peripheral blood mononuclear cells.[71-74] These activities are consistent with the broader antifibrotic and anti-inflammatory activities observed in animal models of fibrosis and in vitro. [66, 69]

Everolimus

Everolimus is known to be a derivative of sirolimus and is considered an inhibitor of mammalian target of rapamycin (mTOR). It is used as an immunosuppressant to prevent rejection of organ transplants and treatment of renal cell cancer and other tumors. Much research has also been conducted on everolimus and other mTOR inhibitors as a possible targeted therapy for use in several types of cancers. Like the others mTOR inhibitors its effect is solely on the mTORC1 protein complex and not on the mTORC2 complex. This function leads to a hy-

per-activation of the kinase AKT via inhibition on the mTORC1 negative feedback loop while not inhibiting the mTORC2 positive feedback to AKT. This AKT elevation can lead to longer survival in some cell types. Based on this activity everolimus has an important effect on cell growth, cell proliferation and cell survival. It has been observed that mTORC1 action is modulated by several mitogens, growth factors and nutrients.

The two genes TSC1 and TSC2 (which are the genes involved in tuberous sclerosis disease) act as tumour suppressor genes by regulating mTORC1 activity. Therefore the loss or inactivation of one of these genes leads to the activation of mTORC1.[75]

Everolimus binds to its protein receptor FKBP12, which directly interacts with mTORC1 inhibiting its downstream signaling. As a consequence, mRNAs that codify proteins implicated in the cell cycle inhibit tumour growth.[75]

Recent trials have indicated that adding Afinitor (everolimus) to exemestane therapy against advanced breast cancer can significantly improve progression-free survival compared with exemestane therapy alone.[76, 77] However, everolimus increased mortality in cancer patients in some studies.[77-79]

Furthermore, there are two studies that show a different sensitivity to everolimus between patients depending on their genome.[79, 80] In a Phase II clinical trial done in patients with advanced metastatic bladder carcinoma (NCT00805129)[80] they found one person that positively responded to everolimus treatment for 26 months. A genetic sequence was performed for this patient. It was discovered that mutations in TSC1 lead to an increase in recurrence and to an increase in the response time to everolimus. Therefore, it has been determined that everolimus is more efficient in those patients that present somatic mutations in TSC1.[81]

Zotarolimus

Zotarolimus is an immunosuppressant and is considered a semi-synthetic derivative of rapamycin. It was primarily designed for use in stents with phosphorylcholine as a carrier. It was observed that coronary stents reduce early complications and improve late clinical outcomes in patients needing interventional cardiology. However, complications have been observed with stent use, such as the development of thrombosis which impedes the efficiency of coronary stents. Moreover; haemorrhagic and restenosis complications are additional problems that can be observed. Therefore drug-eluting stents have been developed. Stents are bound by a membrane consisting of polymers which releases zotarolimus slowly and its derivatives into the surrounding

tissues. Zotarolimus is an analog made by substituting a tetrazole ring in place of the native hydroxyl group at position 42 in rapamycin. The compound is extremely lipophilic, and therefore has limited water solubility. The poor water solubility prevents rapid release into the circulation (for coronary stents) since elution of drug from the stent will be partly dissolution rate-limited. The slow rate of release and subsequent diffusion of the molecule facilitates the maintenance of therapeutic drug levels eluting from the stent. However; the surrounding tissue has to be considered too. Moreover; its lipophilic property induces crossing cell membranes to inhibit neointimal proliferation of target tissue. Zotarolimus is the most lipophilic of all drug eluting stents (DES) drugs.[82]

Sirolimus

Sirolimus (also known as rapamycin) is a chemical that was discovered as a product of bacteria *Sirolium*, was originally developed as an antifungal agent. However, this use was abandoned when it was discovered to have potent immunosuppressive and antiproliferative properties. It has been shown to prolong the life of mice and might also be useful in the treatment of certain cancers. [83] Sirolimus is not a calcineurin inhibitor, but it has a similar suppressive effect on the immune system. Sirolimus inhibits interleukin-2 (IL-2) and other cytokines receptor-dependent signal transduction mechanisms, via action on mTOR, and thereby blocks the activation of T and B cells. It is known that tacrolimus and cyclosporine inhibit the secretion of IL-2, by inhibiting calcineurin. Sirolimus binds to the cytosolic protein FK-binding protein 12 (FKBP12) like tacrolimus. Unlike the tacrolimus-FKBP12 complex, which inhibits calcineurin (PP2B), the sirolimus-FKBP12 complex inhibits the mTOR (mechanistic (formerly mammalian) target of Rapamycin. Rapamycin directly binds to mTOR Complex 1 (mTORC1). mTOR has also been called FRAP (FKBP-rapamycin-associated protein), RAPT1, RAFT (rapamycin and FKBP target). Sirolimus binds to FKBP12-sirolimus complex and inhibits Tor1 and Tor2. [84-86] There have been numerous studies with sirolimus-eluting stents used for coronary disease.[87-91]. Sirolimus eluting stents have demonstrated that they can inhibit neointimal proliferation when applied next to bare metal stents.[87, 92, 93] Several groups have investigated different combinations of sirolimus and sustain release drugs in order to prolong the positive effect of the stent.[88, 89, 94, 95] Several imaging methods have been also applied in order to evaluate sirolimus stent implantation in the coronary vessels. [91, 96, 97]In the study by Habib et. al. [98] it was observed that metformin impairs vascular endothelial recovery after stent place-

ment in the setting of locally eluted mammalian target of rapamycin inhibitors. Metformin could therefore be administered as an adjuvant treatment for these patients or added in the eluting solution. The administration of granulocyte colony-stimulating factor has been observed to attenuate endothelial dysfunction after sirolimus eluting stent implantation.[99] In the study by Erdim et. al. [100] and Tarantini et. al. [101] there were a difference observed between paclitaxel eluting stents and sirolimus eluting stents. The same was true when sirolimus and paclitaxel eluting stents were compared to bare metal stents.[102]

Paclitaxel

Paclitaxel is used to treat a number of cancers such as; ovarian cancer, breast cancer, lung cancer and pancreatic cancer. Paclitaxel and docetaxel represent the taxane family of drugs. Paclitaxel's mechanism of action involves interference with the normal breakdown of microtubules during cell division. Its common side effects include: muscle and joint pains, hair loss, and diarrhea. Anaemia and infections can occur and can be potentially serious. It should not be used during pregnancy as it often results in problems in the infant. Paclitaxel is used as an antiproliferative agent for the prevention of restenosis (recurrent narrowing) of coronary and peripheral stents; locally delivered to the artery wall. It has been observed that paclitaxel coating limits the growth of neointima (scar tissue) within stents.[103] It is known that paclitaxel targets tubulin. Paclitaxel-treated cells have defects in mitotic spindle assembly, chromosome segregation, and cell division. Paclitaxel stabilizes the microtubule polymer and protects it from disassembly. Consequently chromosomes are unable to achieve a metaphase spindle configuration. This function blocks progression of mitosis, and prolonged activation of the mitotic checkpoint triggers apoptosis or reversion to the G-phase of the cell cycle without cell division. It has been observed that the ability of paclitaxel to inhibit spindle function is generally attributed to its suppression of microtubule dynamics. Moreover; in vitro studies it has been observed that at higher therapeutic concentrations, paclitaxel appears to suppress microtubule detachment from centrosomes. This process occurs during mitosis. Paclitaxel binds to beta-tubulin subunits of microtubules.[104-108] Paclitaxel eluting stents have been used for airway bypass [109] and for coronary vessel implantation.[100-102, 110-114] Paclitaxel solution has been also conjugated with a carrier in order to produce a sustain drug release effect.[115]

Doxycycline

Doxycycline is a broad-spectrum antibiotic of the

tetracycline class that is useful for the treatment of many infections. Doxycycline-metal ion complexes are unstable at acid pH, therefore more doxycycline enters the duodenum for absorption while other earlier tetracycline compounds are released in the upper gastrointestinal tract. Moreover; it was mentioned that food has less effect on absorption than on absorption of earlier drugs with doxycycline serum concentrations being reduced by about 20% by test meals compared with 50% for tetracycline.[116] Expired tetracyclines or tetracyclines allowed to stand at a pH less than 2 are reported to be nephrotoxic due to the formation of a degradation product, such as the hydro-4-epitetracycline which induces the Fanconi syndrome. It is known for doxycycline that the absence of a hydroxyl group in C-6 prevents the formation of this nephrotoxic compound. Tetracyclines and doxycycline itself have to be taken with precaution by patients with kidney injury, as they can worsen azotemia due to catabolic effects.[117] In the study by Huvenne W. et. al. [36] it was observed that doxycycline-releasing stents improved postoperative healing after functional endoscopic sinus surgery.

Sirolimus vs. Everolimus

In the study by Gao R. et. al. [94] novel abluminal groove-filled biodegradable polymer sirolimus eluting stent was investigated versus a durable polymer everolimus-eluting stent: None of the two stents presented positive results after 12 months follow up and none was observed to be superior. Regarding the novel abluminal groove-filled biodegradable polymer sirolimus eluting stent the authors stated that the stent was not inferior to the everolimus stent. The stents were found to be effective mainly for the first nine months. In the study by Smits P. C. et. al. [118] abluminal biodegradable polymer sirolimus-eluting stents were tested versus durable polymer everolimus stents: This time the sirolimus stents were found to be as effective as the everolimus stents. In the study by Harjai K. J. et. al. [110] it was observed that everolimus eluting stents were more efficient when compared to sirolimus and paclitaxel eluting stents at least for 3 months of follow up. Again in the study by Park K. W. et. al. [119] Kitabata H. et. al. [120], Moreno R. et. al. [121], Kozuma K. et. al. [122] and Ko Y-G. et. al. [97] everolimus eluting stents were found to be superior when compared to sirolimus eluting stents.

Zotarolimus vs. Everolimus

In the study by Tandjung K. et. al. [123] no difference was observed between the zotarolimus and everolimus stents in terms of safety and efficiency. However; in the study by Kim S. et. al. [124] although zotarolimus had rapid neointimal healing at 3

months, the zotarolimus stents had a slightly better vascular healing profile at long term 12 months. In the study by Park K. W. et. al. [125] both zotarolimus and everolimus stents showed the same safety and efficiency profile after 1 year follow-up.

Zotarolimus vs. Paclitaxel

In the study by Xu B. et. al. [126] It was observed that zotarolimus stents were more efficient when compared to paclitaxel eluting stents within 12 months of follow up.

Sirolimus vs. Zotarolimus

In the study by Van den Branden B. et. al. [127] sirolimus eluting stents were found to have higher efficiency than zotarolimus stents.

Stent Studies for the respiratory tract

Cisplatin

In the study by Chao YK et al. [35] biodegradable stents made of polycaprolactone were fabricated by a laboratory-made, microinjection molding machine. Initially, in vitro mechanical strength of the stents was compared with the strength of Ultraflex SEMSs. Polylactide-polyglycolide copolymer and cisplatin were coated onto the surfaces of the stents. Elution method and high-performance liquid chromatography (HPLC) analysis were used to examine the in vitro cisplatin release characteristics. In vivo, the stents were surgically implanted into the cervical trachea of white rabbits. Bronchoscopic examination was performed weekly and Cisplatin concentrations in trachea, lung, and blood were analyzed by HPLC. Histologic examination was also performed. The biodegradable stent exhibited mechanical strength comparable to the strength of Ultraflex SEMSs and provided a steady release of cisplatin for 4 weeks in vitro. The in vivo study showed sustained cisplatin levels in rabbit trachea for 5 weeks with a minimum drug level in blood. Histologic examination showed an intact ciliated epithelium and marked leukocyte infiltration in the submucosa of the stented area.

Mitomycin C

In the study by Choong C. K. et al. [128] mitomycin C (MTC) was administered locally after stent placement for airway bypass and blocked granuloma tissue formation for up to a week. In the study by Coppit G. et. al. [129] MTC failed to affect the acute inflammatory response, perhaps secondary to the robust inflammatory reaction created by combining a single-stage laryngotracheal reconstruction (SSLTR) with the local circumferential trauma induced by the Palmaz stent. This may have reduced the beneficial effects of the MTC in this study. However; incorpora-

tion of the auricular cartilage graft the stent was improved, contributing again to improved airway stability. The mechanism of this action is not yet understood, as MTC is considered a potent fibroblast inhibitor and not a promoter of neochondrogenesis. It is possible that this is an effect of MTC not previously described. In the study by Sztano B. et. al. [130] mitomycin C prolonged fibrotic tissue formation for almost 6 weeks in a young boy. On the other hand in the study by Uzomefuna V. et. al. [131] again it did not present a positive antiproliferative effect, however; the authors provide data where the effect might be associated with the patients' age. In the study by Carter J. M. et. al. [132] the positive application of MTC was observed with fewer days of hospitalization. In another study by Kim H. et. al. [133] investigating again the effect of MTC application in congenital choanal atresia as in the study by Carter J. M. et. al. [132] no positive effect was observed in this group. In the study by Cardoso P.F.G. et.al. [109] paclitaxel eluting stents were used for airway bypass. Initial results indicated reduction of hyperinflation and improved pulmonary function and dyspnea. In the study by Choong C.K. et. al. [134] in an animal model prolongation of patency was observed. However; in the study by Shah P.L. et. al. [135] no benefit was observed from these stents for homogenous emphysema. Although a previous study by the same group implicated that these patients might benefit from these stents.[136] In the study by Zhu G. H. et. al. [137] bioabsorbable tubular stents eluting MTC (tracheal) were created and they were found to be superior to silicone stents. This study is very important because it provides data regarding the importance of the stent design in mucus trapping. The authors propose a stent design along with a drug eluting carrier, however; further investigation is needed for the stent design.

Doxycycline

In the study by Huvenne W. et. al. [36] doxycycline drug eluting stents were designed and applied for sinus surgery. It was observed that matrix metalloproteinase-(MMP-9) levels were lower along with bacterial colonization and additionally short time healing was observed.

Carriers designed for coronary, airway and gastrointestinal stents

In the study by Bang S. et. al. [138] paclitaxel-eluting membranes were designed in order to release paclitaxel: Positive results have been observed for more than 15 days after implantation. In the study by Qiu H. et. al. [88] sirolimus bioabsorbable poly-L-lactic acid stents were designed and were ef-

fective up to 28 days. In the study by Deng J. et. al. [89] a nanoporous CREG-sirolimus eluting stent was designed with positive effects between 2-4 weeks. In the study by Christiansen E. H. et. al. [139] a bioluminescence-eluting biodegradable polymer-coated stent was compared to durable polymer-coated sirolimus-eluting stent, however; after 1 year the results did not indicate a superiority of these novel stents. In the study by Gao R. et. al. [94] novel abluminal groove-filled biodegradable polymer sirolimus eluting stent was investigated versus a durable polymer everolimus-eluting stent: None of the two stents presented positive results after 12 months follow up and none was observed to be superior from one another. In the study by Huvenne W. et. al. [36] a doxycycline eluting stent was created from copolymer blocks. It was observed that matrix metalloproteinase-(MMP-9) levels were lower along with bacterial colonization and additionally short time healing was observed. In the study by Chao Y. et. al. [35] polylactide-polyglycolide copolymer-cisplatin stents were designed and a sustainable release was observed for up to 5 weeks. In the study by Lemos P. et. al. [140] using polymer-free phospholipid encapsulated sirolimus nanocarriers stents the drug transfer was feasible to all layers of the vessel wall, achieving high tissue concentration that persisted days after the application. In the study by Seo J-B. et. al. [113] two different types of paclitaxel eluting stents were investigated: The polymer polysulfone (Coroflex) and polymer "Translute" (Taxus). The Taxus stent was observed to be superior to the Coroflex within a 9 month follow up.

Discussion

The inherent growth inhibitory properties of many anti-cancer agents make these drugs ideal candidates for the prevention of restenosis. However, these same properties are often associated with local cytotoxicity such as; fistulas. Therefore a multimodality approach is necessary either with debulking and then stent placement or radiotherapy when appropriate. Performance status, comorbidities, disease extent and anatomical malformations of the patient should be considered.

Preparation is necessary in many cases as airway malformation is observed and therefore 3 dimensional investigation has been proposed.[141] In the study by Ratnovsky A. et. al. [28] the stress of different materials were investigated and the authors proposed a patient-specific trachea model evaluation before stenting the patient. The method of stent application/stress, different material and different tissue (benign/malignant) could probably be assessed one day for each patient before application in order to avoid

adverse effects. Since MTC is an antitumour drug that is used in both benign and malignant tissue formation after stent placement, we suggest that other cytotoxic agents with or without carrier that modulate the release of the drug locally should be investigated.[57] Regarding pirfenidone, we cannot propose further studies when we have tissue formation around the edge of a stent if the underlying disease is cancer, however; it would be interesting to design pirfenidone eluting stents for benign obstructions. In the study by Barone-Rochette G. et. al. [142] data are presented where current technology of drug eluting stents is cost effective and therefore novel stents should be encouraged. An issue to be investigated is whether we should provide the patients with an adjuvant therapy when implanting an airway stent. There is the case of the immunosuppressant rapamycin which was the basis for the development of zotarolimus by Johnson and Johnson. Rapamycin was originally approved for the prevention of renal transplant rejection in 1999. There is evidence for coronary stents that when metformin is administered impairment of vascular endothelial recovery is observed. More studies should be performed towards this direction. Another issue is the adverse effects of the drugs that are conjugated with the stent. There is a case reported where a zotarolimus eluting stent induced hypersensitivity pneumonitis.[143] In the study by Iwata Y. et. al. [99] granulocyte colony-stimulating factor was administered and it was observed that endothelial dysfunction was attenuated after sirolimus eluting stents implantation. Again in the study by Rhew S. H. et. al. [144] repeated catastrophic multi-vessel coronary spasm was observed after zotarolimus-eluting stent. In the study by Zhu G. H. et. al. [137] bioabsorbable tubular tracheal stents eluting MTC were created and found to be superior to silicone stents. This study is very important because it provides data regarding the importance of the stent design in mucus trapping. The authors propose a

stent design along with a drug eluting carrier, however; further investigation is needed for the stent design. 5- fluorouracil (5-FU) nitinol stents have been used for the gastrointestinal tract, and could be investigated for the respiratory tract.[145] There are currently novel methods for evaluating the concentration of paclitaxel and 5-FU simultaneously [146], moreover; novel amphiphilic copolymers have been designed to control the drug release such as; 5-FU.[146-148] (Figure 3, Tables 1-2)

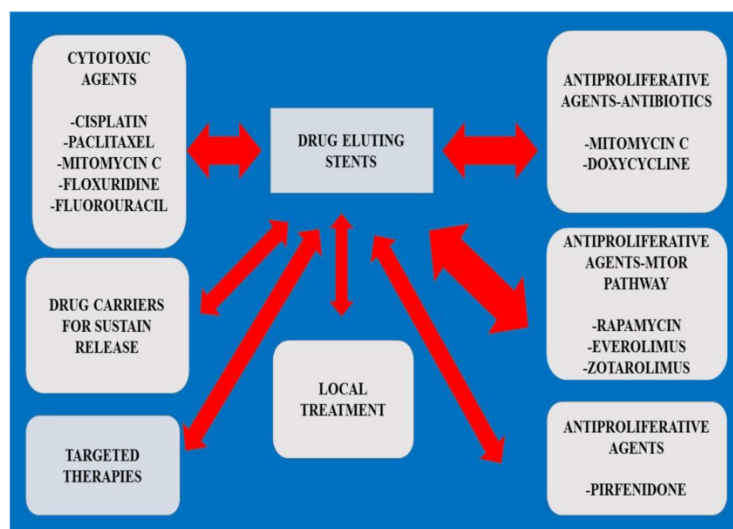
In our mini review we investigate the current knowledge from the coronary drug eluting stents and we present also a comparison between the different materials. We are trying to create a bridge between this knowledge and the data that we obtained from eluting airway stent techniques. There has not been much effort towards stents for lung cancer patients. The main reason is that patients usually have a low performance status when stents are applied usually as palliative treatment. Moreover; interventional pulmonology has many tools for rapid local control. However; a long term local therapy through airway stents for these patients is welcomed. Going through the literature we believe that an ideal airway stent should (1) possess sufficient strength to perform its mechanical function, (2) be biocompatible so that the material breakdown process will not cause any tissue irritation, (3) be biodegradable (no need for removal after serving its purpose), and/or (4) provide effective pharmaceuticals for a sustained period of time. Before stent placement we propose investigation of the airways with computertomography scans and bronchoscopy in order to choose the best stent design and make the appropriate intervention. Finally, the type of lung cancer should direct us to choose the appropriate drug in order to invent drug eluting stents. Agents effective against specific types of lung cancers have been found, such as perimetrexed for adenocarcinoma or TKIs for EGFR or ALK positive patients.

Table 1. Stent studies (In the result section the referenced time indicates the time where the first positive results were observed.)

Author	Subject	Drug	Result	Ref
Chao Y.K. et. Al.	animals	Cisplatin with carrier	5 week with apoptosis	35
Choong C.K. et al.	animals	Mitomycin C	1 week	129
Coppit G. et. al.	animals	Mitomycin C	No effect	130
Sztano B.et. al.	human	Mitomycin C	6 weeks	131
Uzomefuna V. et. al.	human	Mitomycin C	No effect	132
Carter J. M. et. al.	human	Mitomycin C	Less hospitalisation days	133
Kim H. et. al.	human	Mitomycin C	No effect	134
Cardoso F.G.P. et. al.	human	Paclitaxel	Positive effect (emphysema application)	110
Choong C. K. et. al.	animal	Paclitaxel	Prolongation of patency	135
Shah P.L.et. al.	human	Paclitaxel	No benefit, however; safe	136
Huvenne W. et. al.	human	Doxycycline	Shorter healing time, less bacterial colonization, lower MMP-9 levels	36

Table 2. Carriers designed for coronary and airway stents.

-Paclitaxel eluting stents
-Sirolimus bioabsorbable poly-L-lactic acid
-Nanoporous CREGES (Sirolimus)
-Biolimus-eluting biodegradable polymer-coated stent
-Novel abluminal groove-filled biodegradable polymer sirolimus eluting stent
-Doxycycline eluting stent was created from copolymer blocks
-Polylactide-polyglycolide copolymer-cisplatin
-Polymer-free phospholipid encapsulated sirolimus nanocarriers
-Bioabsorbable tubular stents
-Amphiphilic poly(ϵ -caprolactone)-poly(ethylene glycol)-poly(ϵ -caprolactone) (PCL-PEG-PCL) copolymers
- trilayered Poly(ϵ -caprolactone) (PCL)-based film with a coating layer (CL), a drug-storing layer (DSL)

**Figure 3.** Drug eluting stents algorithm.

Conflict of Interest

None to declare.

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