Techniques for intratumoral chemotherapy of lung cancer by bronchoscopic drug delivery

Research Article

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Abbreviations: 5-fluorouracil, (5-FU); computerized axial tomography, (CAT); endo-bronchial intratumoral chemotherapy, (EITC); endoscopic ultrasound bronchoscope, (EBUS); intratumoral, (IT); Sentinel lymph nodes, (SLN)

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Summary

The objective of this review is to provide a detailed description of the technique for a new non-systemic therapeutic modality for NSCLC lung cancer chemotherapy. Described here is the technique for intratumoral injection of one or more cytotoxic drugs directly into tumor tissue through a flexible bronchoscope by means of a needle-catheter. The procedure is termed “endo-bronchial intratumoral chemotherapy (EITC)”. EITC is a loco-regional form of chemotherapy as well as an ablative cytotoxic procedure for removal of endobronchial tumor bulk for NSCLC lung cancer that presents with bronchial obstruction. In addition to the advantage of tumor burden reduction inside the airway lumen, intratumoral delivery of cytotoxic drugs may be regarded as an improved neoadjuvant therapy for use prior to irradiation and/or surgery. EITC differs significantly from conventional intravenous chemotherapy by virtue of the localized non-systemic route of drug delivery. The advantages include: precise delivery of a drug superdose directly to the tumor mass (a dose impossible to deliver safely by normal systemic chemotherapy), and little systemic drug toxicity (in contrast to systemic intravenous drug delivery which is severely dose-limited due to general toxicity). Future multi-center randomized clinical trials will be essential to confirm the short-term and long-term beneficial effects of EITC as a therapeutic strategy for more effective NSCLC treatment. Clinical studies should address the potential benefits for neoadjuvant intratumoral therapy of early NSCLC in combination with other treatments such as brachytherapy and/or photodynamic therapy, and surgery.

I. Introduction

Intravenous chemotherapy often leads to severe complications and abandonment of therapy due to systemic toxicity. To overcome this problem, many recent studies have been devoted to alternative modes of delivery for anticancer drugs to decrease systemic toxicity and improve the therapeutic index for approved cancer drugs. Several studies have shown that intratumoral delivery of cytotoxic drugs by direct injection into the solid tumor mass can provide extremely high doses of drug throughout the tumor with minimal systemic toxicity. Direct intratumoral (IT) injection of cancer drugs therefore represents a new treatment paradigm which may be especially valuable for treating lung cancer, especially when complicated by endobronchial tumor mass obstruction. IT injection is readily achieved through a flexible bronchoscope by means of an ordinary needle-catheter. This procedure, termed “endobronchial intratumoral chemotherapy (EITC)” is described here and is important for consideration as a more effective approach to debulking endobronchial tumor obstruction and neoadjuvant chemotherapy of lung cancer (Wagai et al, 1982; Celikoglu et al, 1991, 1997, 2004, 2006a,b; Liu et al, 2000; Celikoglu and Celikoglu, 2003; Seymour et al, 2006). Our objective is to update information concerning clinical techniques for the direct injection of cytotoxic drugs into endobronchial malignant tumors in order to instruct bronchoscopists and interventional pulmonologists and to facilitate the use of this treatment modality.
II. Method

For bronchoscopic intratumoral injection, patients undergo routine bronchoscopy through any type of standard flexible bronchoscope under local anesthesia in a fully equipped endoscopy suite; at either hospital or outpatient clinics. In addition to a bronchoscopist, the procedure requires 2 dedicated assistants.

The IT injection technique consists of the following steps:
1. Bronchoscopy, to visualize the lesion to be treated.
2. Introduction of a needle-device through the working channel of the bronchoscope.
3. Insertion of the needle into the lesion and injection of drug into the tumor tissue.
4. Repeated needle insertions, as many as considered appropriate to completely perfuse the tumor mass.
5. IT drug injections usually performed weekly. In patients previously treated by standard cancer therapies, EITC can continue up to one to two months as deemed necessary. In newly diagnosed patients, after 4 weekly injection sessions standard cancer treatments may be administered.
6. At end of each bronchoscopic injection session, removal of drug induced necrotic debris may be appropriate using mechanical dissection or other ablation techniques accompanied by irrigation and aspiration.

A. Criteria for patient selection and eligibility

Patients treated for non-small cell lung carcinoma are eligible for endobronchial intratumoral chemotherapy by bronchoscopy based on the following criteria:
1. Patients present with inoperable lung carcinoma and/or recurrent disease
2. Patients present with symptomatic airways obstruction with symptoms such as coughing, shortness of breath, post-obstructive pneumonia or atelectasis
3. Occlusion or partial occlusion of bronchus
4. Prior surgery is not a contraindication
5. Disease verified by bronchoscopy
6. Patients may be receiving systemic chemotherapy and/or radiation
7. No age limitation
8. Metastatic disease may be present
9. Require informed consent
10. Not eligible if patient has predisposing factors for diagnostic bronchoscopy

It is important to note that EITC is intended to serve as a loco-regional neoadjuvant treatment.

B. Staging of NSCLC and EITC Treatment

EITC may be used for palliative debulking at all stages of NSCLC (from Stage I to Stage IV) including all patients who had been previously treated by other conventional modalities and who have relapsed with endobronchial obstructive tumor growth. In cases of advanced and previously treated NSCLC, the use of EITC usually benefits the quality of life but no evidence is available for prolonged survival. For newly diagnosed NSCLC at all stages, EITC can be useful as a neoadjuvant therapy or a sensitizer (with intratumoral Cisplatin) for radiotherapy. In these cases, prolonged survival may be achieved. Here too, EITC may be effective for down-staging NSCLC by removal of tumor bulk, clearing the airways and bronchus, and enabling surgery for patients previously indicated as inoperable.

C. Preparation of patients

Before carrying out intratumoral chemotherapy through a bronchoscope, routine clinical data is of course obtained from patients, including arterial blood gases, coagulation parameters, and blood biochemistry. The chest radiography and computerized axial tomography (CAT) scan of the chest and upper abdomen should be carefully reviewed to locate with precision the extent of the extraluminal localization of the tumor. If it is considered necessary, a PET scan and a mediastinoscopy should be done. If available, though not mandatory, the use of an endoscopic ultrasound bronchoscope (EBUS) may be helpful in some cases to locate any extra luminal malignant growth IT treatment. Auto-fluorescence bronchoscopy, if available, may also be useful to define the margins of malignant infiltration on the bronchial mucous membrane.

An intravenous access site is established, and normal saline is infused during the procedure. Standard monitoring includes an electrocardiogram, non-invasive blood pressure recording and oxygen saturation. Supplemental oxygen is administered nasally as deemed necessary. Topical anesthesia of the oral-nasal-pharynx is achieved with 4% lidocaine. Conscious sedation is achieved with 3-5 mg intravenous midasolam and meperidine.

D. Bronchoscopic complications

Bronchoscopy may be generally regarded as quite safe and well tolerated if performed by an experienced bronchoscopist. Infrequent serious complications are usually associated with patients who have predisposing health factors:
1. a history of asthma may result in bronchospasm
2. infection may occur in immunocompromised patients
3. superior vena cava obstruction predisposes to laryngeal edema and bleeding
4. ischemic heart disease and dysrhythmias are contraindications for bronchoscopy
5. bleeding diatheses may give excessive bleeding when biopsy specimens are taken
6. drug allergies should be noted and anticoagulants and/or cardiorespiratory drugs may need to be stopped

A retrospective study by Credle and colleagues indicated a complication incidence of 0.45% and 0.01% mortality for bronchoscopy (Credle et al., 1974). However, as might be expected, patients with preexisting infections often exhibit a significant incidence of post-bronchoscopy infection and pneumonia. Antibiotic treatment is therefore needed for patients at risk for infectious disease complications.

Some degree of airways obstruction and hypoxemia is inherent in bronchoscopy. We therefore recommend use of supplementary oxygen through the bronchoscope during EITC. This is mandatory for all patients with oxygen tension of 70 mm Hg or less. A single nasal oxygen delivery catheter is convenient for this purpose. Supplementary oxygen should be continued in these patients for at least two hours after the EITC procedure.

E. Bronchoscopic EITC Procedure

The flexible bronchoscope is passed trans-nasally or orally and introduced into the trachea in the usual manner. A full inspection of the tracheal-bronchial tree with conventional white light and auto-fluorescence, if available, is completed. Biopsy specimens would have been taken previously from the tumor to confirm the diagnosis. The biopsies from the sites proximal and distal to the lesion should also have been obtained to define tumor margins histologically. The lesions to be treated are inspected to determine whether they are projecting or bulging into the airway lumen or infiltrating the mucous membrane, and to define the position and extent of stenos or extrinsic compression that may exist. Tumor volume is estimated visually from visible length-width-height measurements over the bronchial surface. The volume of extra-luminal localization of the tumor is estimated from CAT scan or EBUS.
F. Handling of the needle device in the bronchoscope working channel

1. Characteristics of “the needle-device” used for intratumoral injection.

The needle-device consists of a needle-catheter placed in an outer jacket or sheath (steel or plastic). The needle-catheter consists of a metallic needle attached to the end of a plastic catheter. The placement of the needle-catheter within a sheath is to prevent damage to the working channel by the sharp pointed needle during advancement into the working channel of the bronchoscope. During advancement in the working channel, the needle must be retracted into the sheath or outer jacket. Conventional needle devices designed for “transbronchial needle aspiration biopsy” or an “esophageal sclerotherapy catheter”, which are normally available in all endoscopy departments are quite suitable for the procedure.

2. Selection of the size and length of the needle according to the morphology of lesion

The needle size and the length will vary according the type and extent of the tumor growth. For endo-luminal exophytic, polypoid and bulgy tumors inside the airway lumen, 19-21 gauge and 10mm length needles are required. Mucosal, sub-mucosal or mural tumor growths usually require 23-25 gauge and 5mm length needles. Longer needles are best for trans-bronchial injection in extra-mural compressive obstructions because of the long distance from lesions. Therefore, for injecting peribronchial masses or extramural hilar and subcarinal lymph nodes adjacent to the bronchial wall, 21 gauge and 15mm or longer needles are most useful with a stiffer catheter.

3. Plastic needle

A unique needle made entirely of plastic without any metallic ending appears to be particularly useful for peripheral applications. It consists of an outer sheath and inner plastic catheter with a sharpened, beveled tip. The inner catheter can be withdrawn into the sheath during passage through the bronchoscope. The advantage of this needle lies in its lack of the rigid section that is characteristic of metal needles. As a result, plastic needles can generally be passed around sharper bends inside the working channel of bronchoscope than metal needles. This property is particularly useful in injecting upper lobe apical segment and lower lobe superior segment lesions and is also useful for other distally localized tumors.

4. Placement of the needle device in the bronchoscope working channel

Initially, the bronchoscope is introduced into the bronchial tree in the conventional manner to visualize the lesion. Then, the needle-device is put into the entrance hole at the proximal aperture of the bronchoscope working channel with needle-catheter retracted in the sheath. The needle device is then advanced slowly into the working channel.

As a precaution, it is advisable to pass the needle device through the bronchoscope channel with little or no distal tip deflection of the bronchoscope. The bronchoscope can then be flexed as needed once the distal end of the sheath is visible and out of the working channel. When the tip of the sheath is visualized out of the distal end of the bronchoscope working channel, it is forwarded further until the tip of the sheath is approximately 20 mm above the area to be injected. The needle-catheter itself can then be forwarded from its sheath until the needle is seen to be entirely uncovered. We emphasize that the metal needle should be forwarded from its sheath only after the distal end of the plastic sheath is visible through the bronchoscope. At this point, it is helpful to withdraw the sheath into the bronchoscope working channel so that only the needle remains exposed. This maneuver allows the bronchoscope body to support the needle, so preventing the tubing from kinking and giving the operator greater control over the exact placement and advancement of needle. At the moment when the needle is uncovered, an assistant fixes the needle device manually at the proximal aperture of the bronchoscope working channel, so that both hands of the operator are free. This way, one hand of the operator can direct the tip of bronchoscope with the lever and the other hand can push the body of the bronchoscope with the needle uncovered at its distal end. The entire bronchoscope body is then pushed until the tip of needle contacts the targeted tumor area. The needle is then embedded into the tumor tissue to a depth appropriate for injection of drug into the tissue.

G. Injection of the drug

1. Mode of insertion of the needle into the lesion

Injections of drugs are made directly into the targeted tumor tissues: endoluminal mass, mucosal, sub-mucosal, intramural, peribronchial infiltrative lesions or extra-bronchial locations of the tumor growth.

The mode of insertion of the needle may be varied depending on the location, form, and appearance of the lesion to be treated. If the bronchoscopic appearance of the tumor is a polyoid or exophytic mass protruding in the bronchial lumen then the needle is inserted vertically into the tumor and adjacent bronchial mucous membrane (Figure 1). When a malignant lesion is seen as a slightly protruding infiltration above the surface of bronchial mucous membrane or as an infiltration in the sub-mucosal area or elsewhere within the airway wall, the needle is inserted into the lesion at an oblique angle of approximately 45 degrees (Figure 3). In the case of extramural disease causing an extramural compressive obstruction of the bronchial lumen (either by a tumor mass or by a conglomerate of metastatic lymph nodes adjacent to the tracheal-bronchial tree), then the needle is inserted at the wall of the airway at an angle of about 60-90 degrees (Figure 4).

Once the needle is embedded into the tumor tissue; a syringe loaded previously with the drug is placed at the proximal end of the needle-catheter and the assistant starts the injection. To obtain the best therapeutic advantage for this IT drug delivery, it is desired that the drug fully perfuse the entire tumor mass.

For protection of the maintenance personnel from the any probable adverse effects, the syringes are loaded with cytotoxic drugs beforehand in the oncology department under special hoods.

2. Procedures to achieve complete tumor perfusion of drug during injection into tumor tissue

For complete dispersion of the drug solution throughout the tumor mass, the following technique may be useful:

1. The total volume of the drug, calculated according the volume of tumor, should be injected by repeated injections at several insertion points on the tumor surface until the total volume of drug is administered. Approximately, 0.50 ml of the drug solution should be injected at each insertion site.

2. After injecting a 0.50 ml aliquot of the drug solution at one insertion site on the tumor surface, the injection is stopped, the needle is withdrawn entirely from the tumor; and is then embedded at another location. After injecting another 0.50 ml aliquot, injection is stopped again; the needle is removed, and is again embedded at another site. These repetitive injection maneuvers are repeated several times (3-6x) until the entire desired total dose is delivered.

3. In order to obtain the most complete tumor perfusion of the drug, the following technique may also be useful: after embedding the needle into the tumor with the assistant pushing
the piston of the syringe to inject drug, the needle is moved up and down by the operator in a fanning manner in the tumor mass.
4. To avoid spillage and leakage of drug into the airway lumen during removal of the needle from the tumor mass by the operator, the pressure applied to the piston of the syringe by the assistant is halted and the piston is pulled back slightly to create a small negative pressure.

**Figure 1.** Shows the needle inserted vertically into an endoluminal polypoid or exophitic mass.

**Figure 2.** Shows the removal of tumor residues (debridements) by mechanical resection with forceps. The locally injected drug kills the malignant cells but does not remove them. The necrotic residues are therefore removed by mechanic debridement with forceps and facilitates delivery of additional cytotoxic drugs further into the tumoral mass if necessary.

**Figure 3.** Shows the injection of the drug into tumor infiltrating the bronchial wall after removal of the endo-luminal component of the tumor mass.

**Figure 4.** Shows the injection of cytotoxic drug into a tumor that causes a compressive airway obstruction with intact bronchial mucous membrane. No bronchial fistula develops after intratumoral chemotherapy.
This procedure of repeated injections at different tumor sites, accompanied by up and down needle movements in a fanning manner provides for reasonably uniform dispersion of drug throughout tumor mass. After completing the delivery of the total volume of the drug, the needle is retracted into its sheath to prevent damage to the operating channel of the bronchoscope and then the entire needle-device is pulled back from the operating channel of the bronchoscope.

After removal of the needle device from the bronchoscope working channel, irrigation and aspiration may be appropriate to avoid any local adverse effects of the drug due to any drug leakage.

3. Post procedure clean-up of bronchoscope working channel

At the completion of the bronchoscopic drug injection procedure, it is advisable to aspirate

1 liter of saline through the working channel of the bronchoscope in order to remove any remaining drug. The entire bronchoscope is then cleaned in an automated cleaner.

H. Volume of cytotoxic drug solution to be injected into tumor tissue

The volume of the solution to be delivered by intratumoral injection and the dose of the drug to be administered are calculated from the estimated volume of the tumor (not according to the body weight of the patient).

A volume of 0.5 ml of drug solution is usually ready injected for each cubic centimeter of the tumor volume.

Exophytic or polyoid endobronchial tumor volume may be approximated from the bronchoscopic view. The volume of any existing extramural or extra bronchial component of the tumor may be estimated from previous CAT scan or EBUS by the equation (0.5xLxWxH) where “L” is the greatest length; “W” is the greatest width, and “ H” is the greatest depth or height of the tumor (Monga et al, 2000). A total solution volume of about half the estimated tumor volume is usually safely injected into the tumor tissue (at several injection sites) without leakage.

I. Characteristics of cancer drugs used for intratumoral chemotherapy

Preferred cytotoxic drugs for IT injection should not induce significant local necrotic changes in the normal mucosa, should have a normal pH of approximately 7.4, and should exhibit direct anti-neoplastic activity. Drugs that require hepatic activation (i.e. cyclophosphamide) are not suitable for intratumoral injection. For intratumoral injection, standard approved anticancer drugs in solutions for intravenous administration are used. Current research is also being devoted to the preparation of polymer-drug compositions that can enhance drug stability and prolong intratumoral activity with more limited diffusion away from the injection tumor.

Injectable drug-loaded nano-meso-microspheres, liposomes, and polymer gels (i.e. collagen or alginate gels) promise to offer improved therapeutic IT efficacy in the future (Goldberg et al, 2002, 2006; Almond et al, 2003). Until such modified drugs are available for clinical use, currently approved aqeous I.V. drug solutions are useful for IT chemotherapy.

Celikoglu and colleagues have studied in 1997 mixed drug regimens composed of methotrexate, bleomycin, mitoxantrone, mitomycin C, and 5-fluorouracil (5-FU) for intratumoral injection (Celikoglu et al, 1997). Celikoglu and colleagues also studied in 2003 5-FU alone at higher doses for IT treatments with satisfactory debulting results (Celikoglu and Celikoglu, 2003). Liu, has reported the use of carboplatin for intratumoral chemotherapy with favorable results (Liu et al, 2000). Long acting formulas of cisplatin, mitoxantrone, carboplatin and paclitaxel are under investigation for intratumoral chemotherapy (Harper et al, 1999; Goldberg et al, 2006).

J. Intratumoral Cisplatin injection for local neoadjuvant chemotherapy (prior to irradiation or surgery) in patients with NSC lung cancer presenting with bronchial obstruction

Recent clinical trials with systemic cisplatin chemotherapy have shown cisplatin to be one of the most active agents against NSCLC. It is therefore the most frequently used cytotoxic drug in conventional systemic combination chemotherapy (Sandler et al, 2000; Gatzemeier et al, 2001). It has also been demonstrated that intravenous cisplatin can sensitize malignant cells to irradiation (Shake-Konig et al, 1994; Yapp et al, 1998). Moreover, cisplatin in a collagen gel has been reported to successfully treat a variety of localized malignant tumors. Cisplatin has been administered by direct endoscopic injection for palliation of obstructive cancer of the esophagus (Monga et al, 2000), by IT injection for head and neck cancers (Burris et al, 1998), by CAT-scan guided IT injection into malignant liver tumors (Engelmann et al, 2002) and by endoscopic IT injection into gastric tumors (Monga et al, 1998).

Endobronchial intratumoral chemotherapy with cisplatin was initiated by Celikoglu and colleagues for lung cancer patients presenting with bronchial obstruction. In previously untreated inoperable lung cancer patients, satisfactory results were obtained using bronchoscopic IT injections as a neoadjuvant chemotherapy prior to irradiation. Significant relief of bronchial obstruction was seen for 75% of treated patients (Celikoglu et al, 2006a). Celikoglu and colleagues have also shown that intratumoral chemotherapy with cisplatin can result in down-staging NSCLC and enable surgical intervention (Celikoglu et al, 2006b).

A. Cisplatin dosage for intratumoral injection at each IT injection session

Cisplatin has been used in the solution form which is available for intravenous administration (Celikoglu et al, 2006a,b). Cisplatin may be utilized at a concentration of 2 or 4 mg/mL. That means, if a 0.5 ml aliquot is injected for each cc of tumor volume; 1 or 2 mg cisplatin is administered at each treatment session. Although the total dose of cisplatin delivered by intratumoral injection is based on the estimated total volume of the tumor mass, it is preferable that a total dose of not more than 40 mg of cisplatin be injected at each IT injection session (Celikoglu et al, 2006a,b).

K. Scheduling of injection sessions and duration of intratumoral chemotherapy treatment

1. For previously untreated patients

For previously untreated patients, cisplatin may be administered four times at weekly intervals (on days 1, 8, 15 and 22). Three to seven days after the last session of intratumoral chemotherapy, irradiation may be initiated if deemed appropriate (Celikoglu et al, 2006a,b). In operable cases or in cases where down-staging was achieved after EITC, surgery may be carried out 3-7 days after termination of IT treatment (Celikoglu et al, 2006b).

2. For patients previously treated by surgery, by extra-beam irradiation, or by systemic chemotherapy

For such patients, IT chemotherapy is carried out at weekly intervals. If a response is obtained, EITC therapy can continue for 6-8 weeks or longer until the disappearance of the
endobronchial tumor growth. If there is no positive response after 3 weeks of weekly EITC injections, the IT therapy may be stopped. Other endobronchial ablation techniques such as laser photoresection, electrocautery, cryotherapy may then be tried. In cases of poor response to other interventional bronchoscopic procedures, it may be appropriate to evaluate EITC.

3. Patient follow-up
For those patients previously treated by other standard cancer therapies, if bronchial obstruction has been relieved by IT chemotherapy, follow-up bronchoscopic examinations should be performed at least every three months. Biopsy specimens of the treated areas are taken and examined by the same pathologist who examined the initial specimen. It is advisable to use autofluorescence to detect any tumor recurrence. If tumor recurrence is noted, patients may be indicated to receive additional IT treatment. The same follow-up protocol is advised after radiotherapy.

L. Effects of intratumoral delivery of cytotoxic drugs on tumor tissue

1. Early effects
The tumor mass is usually seen through the bronchoscope as an endo-luminal protruding polypoid mass. While injecting the drug solution, the tumor around the needle becomes swollen, pale and whitish. This is probably due to edema of the tumor tissue and compression of blood vessels inside the tumor by the volume of injected solution.

2. Delayed effects
Three to seven days after intratumoral drug injection, bronchoscopic examination normally reveals some reduction of the tumor mass. Tumor surfaces appear to be covered with a white-yellow gel-like substance. Histopathology indicates the presence of necrotic tissue, devitalized tumor cell residues, fibrin coagulum, dissipated secretions and white blood cells. In some cases, weeks to months later, the tumor may disappear completely leaving a grey colored scar tissue in place of the tumor (Celikoglu and Celikoglu, 2003; Celikoglu et al, 2006a,b). This necrotizing effect of locally administered cytotoxic drug is presumably due to contact and interaction of the malignant cells with the extremely high concentration of drug to which the tumor is exposed by direct drug injection (Goldberg et al, 2002, 2006).

A few days after IT drug delivery the texture of the malignant tissue may appear to soften and become brittle and is then easily separated into small fragments. This is likely due to an early necrobiosis or necrosis. As a result of the early necrosis and reduction in size of the tumor mass, in some cases the diameter of the airway passage may be amplified and symptoms alleviated even after the first session of treatment. In such cases, it is also possible to observe rather rapid recovery from accompanying pathology, i.e. atelectasis or obstructive pneumonia. When the tumor growth is present as an infiltrative process with slight protrusion on the surface of the bronchial mucous membrane, the infiltrative processes improve markedly after drug injection. This infiltrative tumor growth is usually converted to a white-yellow “membrane-like” substance (Celikoglu and Celikoglu, 2003; Celikoglu et al, 2006a,b).

M. Haemostatic effect of intratumoral injection of cytotoxic drugs
Clinical observations indicate that intratumoral injection of cytotoxic drugs may also provide a haemostatic effect on the tumor bulk. The bleeding tendency of tumor tissues is thereby often reduced after IT drug injection. In such situations, piecemeal resection of tumor debris with forceps does not provoke further bleeding (Figure 2).

It is reasonable to regard the following factors as contributory to the haemostasis:
1. Vasocclusion of small vessels in or around the tumor growth due to reaction with a very high concentrations of the cytotoxic drug;
2. Oligemia caused by the compression of small vessels in the tumor due to the volume of drug solution injected into the restricted intratumoral volume;
3. Occlusive intravascular thromboses in the tumor vessels.

The haemostasis is advantageous in that it facilitates resection of the necrotic tumor mass with forceps and removal of tumor tissue debris (Celikoglu and Celikoglu, 2003; Celikoglu et al, 2006a,b).

N. Removal of residual tumor debris by ablation techniques after EITC of obstructive endo-luminal tumors
Although a significant reduction in tumor size may be affected by IT chemotherapy and may thereby be sufficient to alleviate symptoms, tumor size reduction in some cases may not adequately restore the airway passage as quickly as desired. Cytotoxic drug injection into the tumor kills the cancerous cells but does not immediately result in elimination of necrotic residues. Thus, in urgent life threatening situations with severe dyspnea where immediate obstruction relief is obligatory, tumor cell debris, necrotic residues, and fibrin plugs should be removed by other means. In such cases, endobronchial ablation procedures such as mechanical resection, laser photoresection, electrocautery or cryotherapy should be utilized.

The limited haemostatic effect provided by IT drug injection often facilitates the removal of tumor residues by mechanical resection with forceps without serious bleeding (Figure 2). Piece by piece resection with forceps can therefore be useful for debulking of tissue residues after IT endo-bronchial chemotherapy (Celikoglu and Celikoglu, 2003; Celikoglu et al, 2006a,b).

O. Adverse effects of intratumoral chemotherapy
During injection of the cytotoxic drug, patients report no pain or other disturbing sensations. Injection of the drug into normal mucous membranes around the malignant tissue also does not cause any important symptoms. No adverse effects such as irritation or necrosis have been noted due to contact of the drug solution with the surface of normal bronchial mucous membrane. After IT chemotherapy, transient moderate chest pain, a slight sensation of nausea, and/or a moderate fever of one day duration may be noted. No other important systemic or local side effects are observed. No systemic toxicity such as interstitial pneumonia, bone marrow suppression, worsening of inflammatory findings or hair loss has been observed. Nephrotoxicity, neurotoxicity, and myocardiitis, which are commonly associated with systemic intravenous administration of drugs such as cisplatin, are also not seen (Liu et al, 2000; Celikoglu et al, 2006a,b).

P. Dispersion of drugs in the tumor mass

1. Drug distribution by diffusion
The success of intratumoral chemotherapy is dependent upon relatively complete permeation of the injected malignant lesion with a very high concentration of drug with minimal rapid diffusion from the injected tumor tissue into the systemic circulation.

Protocols involving repetitive injections and weekly treatments for several weeks are designed to maximize the probability that all tumor cells in the injected lesion are subjected to lethal drug concentrations. Fortunately, although small drug molecules may associate with tumor tissues by inherent tissue
affinity and by DNA binding, some diffusion away from the injection sites via the extra-cellular tumor tissue fluid can also occur to facilitate tumor perfusion by most drugs. The extent of such diffusion is proportional to ratio of the injection site drug concentration and the drug concentration in the surrounding tumor tissue. When there is a relatively uniform drug concentration within the tumor tissue, drug diffusion out of the tumor will be dependent on the rate of drug passage into the lymphatic and vascular systems.

Repeated IT injections facilitate complete permeation of drug into the entire tumor mass. The drug transport process is also affected by the relative porosity of the tumor tissue with some variation in such porosity according to tumor type and size. Clinical CT scan observations have demonstrated that even when only a small part of the tumor is visible by bronchoscopy, the injection of cytotoxic drugs into an endoluminal portion of the tumor is effective in also decreasing the size of the extramural part of the tumor. This suggests that anticancer drugs injected into one portion of the tumor may diffuse throughout the tumor mass (Goldberg et al, 2002, 2006).

2. Sentinel lymph node drug perfusion (drainage of drug molecules via afferent lymphatic vessels)

Sentinel lymph nodes (SLN) are the first lymphatic drainage site of a tumor and the likely site of initial metastatic tumor cell dissemination (Tiffet et al, 2005). Although the overall prognostic significance SLN micro-metastases in early lung cancer remains unclear, recent studies suggest that for larger and potentially resectable lung cancers there is a significant 5-year survival advantage in patients with adenocarcinoma who do not have SLN micro-metastases when compared to patients with SLN micro-metastasis (62% with metastasis vs. 86% with no metastasis) (Wu et al, 2001).

IT injected drug molecules can be transported by afferent lymphatic vessels into the sentinel and draining lymph nodes. Such drug transport to the lymph nodes may be expected to have a valuable therapeutic effect by eradication of lymphatic micro-metastases. Clinical studies performed using pre-surgical radioisotopes, blue dye techniques, and even the blue cancer drug mitoxantrone, support this view of drug molecule transport from an IT injected site to sentinel and draining lymph nodes (Izbicki et al, 1996; Baitchev et al, 2001; Wu et al, 2001; Lardinois et al, 2003; Tiffet et al, 2005). As also suggested by Lardinois et al, drug injected through the bronchoscope into normal tissues around the tumor is also transported to sentinel lymph nodes. We deduce from this that EITC may have the added advantage of inhibiting metastasis by cytotoxic action on tumor cells which are migrating into the lymph nodes that drain the tumor area (Lardinois et al, 2003).

3. Low systemic concentration of IT injected drugs

Although we have no human clinical data, animal studies have shown that very high doses of cytotoxic drugs (>10-30 times normal intravenous doses) are achieved within tumors by intratumoral injection. However, only minute amounts of IT drug pass into the systemic circulation (Goldberg et al, 2002, 2006). Minimal systemic drug concentrations occur because of several unique aspects of IT injection. Depending on the molecular structures of specific cancer drugs, factors such as drug-tissue affinity, drug instability, rapid drug metabolism, low plasma solubility, and low tissue diffusion rates limit the extent of drug transport into surrounding tissues and vasculature. Furthermore, a major drug transport pathway for IT injected drug molecules is via the afferent lymphatics to the sentinel lymph nodes and then leave lymph glands by efferent lymphatic vessels which ultimately empty into the thoracic duct and right lymphatic duct which then empty into the venous circulation. The amount of drug and the rate of transport into the systemic circulation is thereby so limited that no adverse systemic effects are observed.

IV. Discussion and Conclusions

Reviewed here are the techniques and clinical indications for EITC. It is noted that EITC may be used as a preoperative or neoadjuvant procedure or used concomitantly or sequentially with other standard lung cancer treatments and interventional therapeutic bronchoscopic procedures. EITC is a novel therapeutic paradigm for lung cancer treatment, particularly for widespread application to malignant endobronchial tumor growths. By providing local delivery of cancer drugs, EITC achieves a significant reduction in systemic toxicity with few of the toxic side effects of systemic chemotherapy.

The EITC procedure is not yet used to its full potential. Increased training for interventional pulmonologists in the techniques for bronchoscopic EITC is needed to help broaden clinical perspectives and to make clearer the therapeutic scope and opportunities for EITC. Increased attention should be focused on such less invasive and less toxic treatment strategies for lung cancer.

In a recent study, Nader reported that intratumoral administration of cisplatin, as an adjunct to brachytherapy, was a safe and potentially useful modality to assist in the management of endobronchial tumor obstruction and possibly for long term efficacy. It was concluded that further studies are needed to more fully assess the benefits of this treatment (Nader, 2007).

In addition to the obvious advantage of tumor burden reduction inside the airway lumen, intratumoral bronchoscopic delivery of cytotoxic drugs provides a unique loco-regional neo-adjuvant therapy for use prior to irradiation or surgery (Celikoglu et al, 2006a,b). It is chemotherapy which differs from intravenous chemotherapy only by its local route of delivery. Although the number of clinical studies to date are limited, intratumoral chemotherapy has been found to be advantageous compared to intravenous chemotherapy for effecting efficient tumor regression with minimal side-effects. One example is a comparative clinical study by Liu and colleagues where intratumoral chemotherapy with carboplatin was combined with systemic carboplatin and found to be superior to systemic chemotherapy alone for prolonged survival of lung cancer patients (Liu et al, 2000). In addition to the development of statistically significant survival data, future clinical studies should also encompass: different drug combinations, IT drug dose response, timing of EITC injections, evaluation of drug serum levels vs. time, and mechanistic studies designed to measure T-cell/killer cell activity and tumor-specific immune response.

References


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