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Chemotherapy and the future: microdialysis as a local administration technique

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Summary

Chemotherapy has an important role in cancer treatment. Although there have been developments and good results, chemotherapy still has many limitations mainly due to its toxicity and to the resistance mechanisms of tumour cells. Therefore, besides other important improvements in chemotherapy agents and indications, recent researches have focused on the development of locoregional administration techniques, with which therapeutic weapons can reach the tumour with a higher concentration and fewer side-effects. At present, local chemotherapy includes delivery systems or prodrug strategies, arterial infusions, intraperitoneal administration and aerosolised agents. We will describe a new local cancer chemotherapy method, using microdyalisis procedures, which may revolutionise the actual tumour management because of the higher effectiveness and the absence of side-effects. Finally, the applications and limitations of this technique will be considered.

Introduction

Tumour cells are susceptible to certain therapeutic agents because they have specific characteristics such as unlimited proliferation with loss of apoptosis mechanisms, independence of contact inhibition, anchor mechanisms and growth factors, invasiveness and the ability to originate metastasis, angiogenesis, and incapacity to produce asparagine.

In the first century, tumours which were in an initial stage were treated with colchicine. Until the 20th century, with the discovery of the effects of mustard gas in 1919, few improvements were made in cancer treatment. In 1940, the hormonal treatment in prostate and breast cancer appeared. In the second half of the last century, many cytostatics were developed and, only at the end of that century, scientists started to study new molecules used in targeted therapy.

Today, there are several groups of cytostatics with different actions in the cell. Some of them damage the DNA by an alquilation process or free radicals formation; others inhibit DNA synthesis or function (antimetabolites and topoisomerase inhibitors) or act in the mitotic spindle; finally, there is a group which acts on steroid receptors, both as agonists and as antagonists.

Many cancers resist chemotherapy schemes through different cell mechanisms such as decrease in drug intake, increase in deactivation of the drug, decrease in activation of the drug, increase in repair of the DNA, inhibition of drug binding, overexpression of the target protein and increase in drug out-take [1, 2].

Several strategies have been developed to overcome the resistance mechanisms, including increased doses, but this is accompanied by side-effects. In this context, local chemotherapy appears to be a good treatment option.

Future perspectives in chemotherapy

Although both neoadjuvant and adjuvant systemic therapy have proven to have a high efficacy in reducing the recurrence rate, chemotherapeutic agents have important effects in several organs of the body, namely they can have haematologic, digestive, dermatologic, urinary, cardiac and allergic toxicity. Most of them limit the dosage and the frequency of the therapeutic regimen. In the present, early recognition and treatment of toxicity facilitate good symptom control, prevents treatment-related morbidity, and allows continuation of anti-cancer therapy. Nevertheless, several strategies should be developed in order to achieve better results in cancer treatment.

There is a long road to achieving effective chemotherapy with minimal side-effects. More research work should be carried out to develop more specific drugs and new indications for the present therapeutic agents, to work on new formulations or administration techniques, and to optimise the dosage.

At present, chemotherapy drugs destroy most tumour cells, but there are many relapses. More specific drugs can be achieved by characterising individual genes and tumour biology, and developing tailored and targeted therapies. The actual concept of tumour stem cells should lead to the discovery of more specific drugs which would destroy these cells, allowing us to achieve a highly effective and curative chemotherapy [3].

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For what concerns new indications, neoadjuvant therapies in breast cancer and more recently in gastric and rectal cancers are good examples of the importance of the chemotherapy schedule. Furthermore, some agents can have a good efficacy in tumours in other locations. For example, oxaliplatin, which was formerly used in lung cancer, is now being used in gastrointestinal, breast, bone and soft tissue cancers [4]. In pancreatic cancer, gencitabine has also shown to be better than isolated supportive care [5].

The dose and chemotherapy action can be optimised by recognising the tumour and the drug kinetics, distinguishing if short or long, unique or repeated infusions are more suitable for each case [5]. Moreover, the principal resistance mechanisms can be overcome by developing multidrug resistance proteins inhibitors, improving tumour sensitivity [6]. Finally, the dose can be increased by using new protective drugs or by using local delivering systems.

Local chemotherapy

Most of the clinically approved anticancer drugs are characterized by a narrow therapeutic window because of their high systemic toxicity, in combination with an evident lack of tumour selectivity. The best way of destroying the tumour cells with minimal systemic side-effects is to perform local chemotherapy. Therefore, loco-regional chemotherapy has been proposed as a treatment modality in a number of cancer settings. This can be achieved in different ways, such as delivery systems or prodrug strategies, arterial infusions, intraperitoneal administration, aerosolised agents and microdialysis, which may revolutionise chemotherapy and will be described with more detail.

Prodrugs are chemicals whose release is controlled at the tumour site, and which are transformed in the active form in the same place. Active and passive targeting using tumour-specific ligands or macromolecular carriers have been used as well as release strategies that are based on tumour-specific characteristics such as low pH or the expression of tumour-associated enzymes. Furthermore, other strategies such as antibody-directed enzyme prodrug therapy and the design of self-eliminating structures are also being used [7].

At present, liposomal delivery systems lack the ability to actively release the carried drug and rely on passive diffusion or slow non-specific degradation of the liposomal carrier. To decrease toxicity new strategies should be developed so that liposomal carriers are actively degraded in the tumour tissue. Many promising strategies have emerged ranging from externally triggered light- and thermosensitive liposomes to receptor targeted, pH- and enzymatically triggered liposomes relying on an endogenous trigger mechanism in the cancerous tissue [8]. Nanoparticles also provide a new mode of cancer drug delivery functioning as a carrier for entry through fenestrations in tumour vasculature allowing direct cell access [9].

Arterial infusion of chemotherapeutic drugs has also been studied. For example, hepatic arterial infusion of chemotherapy delivers higher local drug concentrations to unresectable liver tumours with fewer significant systemic side-effects. This chemotherapy administration method is safe and efficacious for improving liver function prior to operative resection of primary colorectal cancer in patients with liver dysfunction due to synchronous and unresectable liver metastases. The aim of this method is to improve patients' clinical condition for later surgical removal of primary colorectal cancer [10, 11].

The use of intraperitoneal chemotherapy, in combination with the systemic one, after surgery is the preferred treatment method for advanced ovarian cancer. It has been administered in clinical trials and some clinical settings for other histologies, such as low-grade gastrointestinal carcinoma and appendiceal carcinoma, which tend to spread locally before invading the bloodstream. Local-regional chemotherapy potentially is an ideal treatment for local spread of those peritoneal carcinomas. This chemotherapy type allows a high concentration of drugs to come into direct contact with tumours and surrounding tissues and organs. Nevertheless, there are still controversial issues regarding the use of IP chemotherapy, namely concerning treatment complications [12].

In primary or metastatic lung cancer, administration of aerosolised chemotherapy via inhalation may also increase exposure of lung tumour to the drug, while minimizing systemic side-effects. Several studies have been performed with good results [13].

Finally, photodynamic therapy is also a way of performing a loco-regional therapy by sensitising a molecule (usually a porphyrin) with a light beam, originating a cytotoxic molecule, which can destroy local tumour cells [14].

Microdialysis

Microdialysis procedures were developed in the seventies with the aim of improving the study of cerebral neurotransmissors. They were performed by placing hollow fibres in brain tissue, which simulate blood vessel function. The technique has expanded and is now available for studies in various animal and human tissues [15].

A microdialysis catheter consists of a double lumen cannula with a semipermeable membrane glued to its end. Perfusion liquid is injected by a perfusion pump in a lumen leaving the catheter by the other one. As in the local membrane there is a continuous diffusion process, the composition of intracanulla fluid reflects the equilibrium between the perfusion liquid and extracellular liquid. This equilibrium is influenced by the differences between solute concentrations, by membrane length, by the pore diameters and by the liquid perfusion rate in the catheter [16].

Microdialysis has been used in oncology to determine pharmacokinetic parameters by measuring the extracellular cytostatic concentrations, after previous systemic administration [17]. More recently, it has been used to quantify growth and regulator factors in carcinogenesis [16].

However, in spite of its unique properties, microdialysis has never been used with a therapeutic purpose. The placement of a microdialysis membrane within the tumour in the extracellular liquid and the perfusion of a drug by a catheter may lead to a higher concentration of chemotherapeutic agents in the tumour with less systemic distribution, significantly decreasing the side-effects. The effectiveness of this procedure may be related to perfusion conditions and tumour characteristics.

Perfusion conditions include the drug concentration, time and number of administrations, perfusion rate, membrane length, pore diameters, and number of catheters and their position within the tumour. All these parameters may be optimised to achieve the best results. Nevertheless, tumour characteristics, namely the size and the type of tumour which may influence the diffusion rate, are unchangeable.

Although our idea is very appealing, some research should be performed in order to develop microdyalisis as a real improvement in chemotherapy administration and to optimise the conditions of this innovative technique.

Placement of a microdialysis membrane within a tumour for therapeutic purposes is a quite simple procedure when tumours are highly accessible, like in breast, skin, vulva, penis and testicular cancers. Nevertheless, the development of some practical abilities may lead to the use of this technique in other types of cancer. Cervical and endometrial cancers as well as some digestive tumours, such as colorectal, oesophageal, gastric and pancreatic cancer, and a few respiratory and urinary tumours can be easily reached by endoscopic procedures. Catheters may be also inserted in prostate cancers by a transrectal approach, in spite of the possibility of fistula formation. Afterwards, brain cancer may be treated by neurosurgical placement of the membrane within the tumour. The membrane may remain in place for some days to allow multiple chemotherapy administrations.

Chemotherapy administration by microdialysis membranes may be used in a few selected cases with a curative intent. Moreover, it may be a good alternative to the systemic approach in neoadjuvant therapies because of absence of the most important side-effects.

The most important limitation of this technique seems to be its uselessness in disseminated tumours, although it may have good results in symptomatic treatment of certain localised metastasis, like secondary brain tumours.

Targeted therapies have been developed during the last decade. They include monoclonal antibodies, inhibitors of vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR) pathways, bevacizumab and erlotinib, respectively, or individual drugs that target both pathways, such as vandetanib [18]. Many of these drugs which target human tumours have been studied in clinical trials, with encouraging results in advanced colorectal cancer, renal cell cancer, breast cancer and non-squamous non-small cell lung cancer, either combined with chemotherapy or in monotherapy [19]. Nevertheless, most of the targeted therapies have very restricted indications, although they seem to have a good effectiveness, because they are accompanied with deleterious side-effects when administered in a systemic way. Hypertension and proteinuria are commonly seen, but the unexpected toxicity of life-threatening hemoptysis has also been observed [20]. This makes careful patient selection especially important for this class of drugs today. Therefore, microdialysis, as a locoregional administration technique, seems to be a more secure way of delivering "targeted agents to the target", and may also amplify the indications of these specific therapies.

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