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Subcutaneous Administration of Anticancer Agents: A Narrative Review

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Abstract

Intravenous (IV) administration is considered as the primary route of administration for many anticancer agents. However, there are some limitations such as the possibility of postinjection infections and catheter failure. Moreover, there is a need for skillful health workers and postinjection hospitalizations, which all bring a financial burden for patients and healthcare systems. Therefore, there is a need for finding a new route without the challenges of the IV injection. Among the different routes of administration, Subcutaneous (SC) delivery of chemotherapeutic agents has attracted much attention. SC route can provide acceptable bioavailability, rapid absorption, and less invasion, and seem to meet the optimal criteria for use as the primary route of administering chemotherapeutic agents. In SC delivery, self-administration is also approved in cases of methotrexate and cladribine. The present study aimed to comprehensively review the current knowledge about using SC delivery of different anti-cancer agents.

Introduction

Conventional therapy for cancer commonly is based on the intravenous (IV) injection of chemotherapeutic agents which need hospitalization. The prevalence of cancer increases with age around the world, as estimated there will be about 26 million new per year, by 2030 [1,2].

Moreover, intravenous administrations may have some challenges and limitations. There is a need for qualified health workers because administration via the central IV route needs an implantable chamber and an injectable formula of chemotherapy agents should be prepared before injection at the hospital [3-7]. Since there is a possibility of systemic toxicity by chemotherapy agents following the IV administration thus in most cases after receiving the IV chemotherapy there is an urgent need for hospitalization and regular monitoring for the early identification of possible toxicity. One of the other limitations in the field of IV administration is catheter failures, which can cause catheter-related bloodstream infections, it is life threatening [8-14].

Therefore, there is a need for finding newly effective administered routes for chemotherapeutic agents which do not require postinjection care and hospitalization without the dangers of the conventional routes and are less costly.

In looking for finding a solution, Subcutaneous (SC) administration due to its advantages, attracts much attention. The main advantage of the SC over the IV is that it is less invasive and much more comfortable for the patient [15,16]. In addition, there is

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no need for hospitalization, even injections can be done by patients without qualified health workers. Furthermore, SC over the oral route shows higher bioavailability (more than 80%) and more satisfactory absorption of the medicine [5,17,18]. Here we aimed to comprehensively review the current literature on the subcutaneous administration of chemotherapy drugs.

Administration routes and effect on absorption

The term absorption refers to drug movement from the administration site to the target center, which depends on its passage through the cell membrane and following that absorption, distribution, metabolism, excretion, and action will occur [19,20]. The four main mechanisms involved in absorption are simple diffusion, active transport, facilitated transport, and passive transport. Passive diffusion is considered the most common type, which refers to the medication movement from a higher concentration to a lower one until the balance is reached [21-25]. However, drug features define its movement across membranes and bioavailability at sites of action which include drug structure, size of the drug molecules, ionization degree, the ability of serum and tissue proteins to bind, and relative solubility in lipids. The term bioavailability refers to the fractional size of drug dosage at the site of action [26,27]. As an example, the absorption of the drug that delivers through oral routes done in the gastrointestinal tract and then passes the liver to reach the systemic circulation. All along this route, the drug undergoes changes (for example, biliary excretion), and if the liver and intestines have a large capacity for metabolic or excretory of the drug, its bioavailability will decrease which all of them call the first-pass effect [28-30].

Enteral

Oral administration is well known as an ancient manner of drug delivery, which still is the most convenient route. This route will follow by the gastrointestinal tract absorption and effect through different factors such as absorption surface area, the flow of blood to the absorption site, the drug's physical form (suspension, solid, or solution), its solubility in water and concentration at the site of absorption. In the case of the solid form of the drugs, their dissolution rate affects the absorption and even may limit it [31,32]. Since the absorption of the drug from the intentional tract happens through passive diffusion, features such as being lipophilic form and nonionized for absorption from the GI tract bring better absorption. The pH is another factor that affects the absorption of the drug from the GI tract, which means that weak acid drugs (pH=1 to 2) have better absorption from the stomach, and the pH range of 3 to 6 has better absorption from the upper intestine. Since the upper intestine has a larger contact surface area (about 200 m^2), thus drug absorption rate will be more than the stomach [33,34]. This route has several advantages in comparison to other routes of drug delivery including convenience, non-invasive, without any pain for patients, without the need for external assistance, cost-effective, without the need for sterile precautions, and available in both solids and liquids. However, the same as all other delivery routes, oral delivery also has some disadvantages such as its unsuitable in emergencies due to the slow onset of action, can't be suitable in the case of patients who are comatose and unconscious, and due to the first past effects of this routs drug absorption is variable [35-37].

Parenteral

Intravenous route

This route is well known as rapid-acting due to the direct access of drugs to the systemic circulation that also brings the bioavailability to about 100%. Intravenous administration is a suitable choice in emergency cases, there is a need for external assistance and sterile precautions, also there is a need for postinjection monitoring of patient's vitals [38-40]. One of the limitations of this route is its need for aqueous solutions because the bioavailability is complete and rapid. Since in this manner, plasma concentrations of drugs as well as their concentration in tissues rapidly increased, always there is a possibility of unfavorable reactions for patients [39,41].

Subcutaneous route

In this manner, due to the physiological features of the subcutaneous layer like rich nerves and fewer vessels, the drug has a slow absorption rate. Moreover, this route isn't suitable for irritant and vesicant drugs due to the numerous nerves. Since this layer is very thin, thus only limited volumes of drug can be used in each injection. However, the main advantage of this route is it's easy for self-administration without the need for an external assistant [40,42].

Bioavailability

This term refers to the amount of drug that reaches the systemic circulation, which is different based on the administration route due to the first-pass effects. Bioavailability is indicated as F which has ranged from 0 to 1. The 0 value means there wasn't any absorption, while the 1 value is referring to the occurrence of complete absorption. Intravenous routes bring 100% bioavailability which means F=1 [43-45].

Subcutaneous versus intravenous

Since the intravenous administration of chemotherapeutic agents leads to adverse effects and financial burdens, the subcutaneous route was further discussed in terms of comfort for the patient [46-48]. However, there is little data in the field on using subcutaneous administration as a potential route with less adverse effects over intravenous. In this manner, chemotherapeutic agents will deliver to the subcutaneous tissue called the hypodermis, which could be a satisfying alternative route in poor venous access patients [49-51]. In addition, in the SC as there is no need for an implantable chamber, thus the risks of postinjection infection have radically decreased. Since SC delivery mostly is a short injection, thus there is no need for post-injection hospitalization and even patients can do the administration on their own without the need to go to the health units. Therefore, this manner will also radically decrease healthcare costs [5, 52-56]. However, the same as the other therapeutic methods, this method also has some limitations like the volume of the drug in each injection, which should be limited to 1-5 ml, and in some cases may need concentrated formulations or separate administration in two different sites. For effective delivery, maybe there is a need for adjuvants in the case of macromolecules like antibodies. Moreover, in comparison to IV delivery, absorption may be delayed that depends on the site of injection including the abdomen, upper arm, or thigh. In some cases, SC delivery can cause erythema or pain in the sites of the injection [57-65]. On the other hand, some anticancer agents such as taxanes and vinca alkaloids are irritant and vesicant and can be stored in the SC tissue with lipophilic properties and cause local toxicity and necrosis at the injection site [66]. The chemotherapeutic agents that are administrated via SC routes are discussed below (Tables 1 and 2).

Table 1: Anti-cancer agents under self-administration for SC delivery.

Agent	Subcutaneous use for	Other diseases	Recommended dosing	Bioavailability	Half-life	Description	Clinical trial
Methotrexate	Acute lymphoblastic leukemia	Breast cancer, leukemia, lung cancer, lymphoma, gestational trophoblastic disease, osteosarcoma	40 mg/m^2	64-90%	5-8 h	Inhibits cell proliferation; Disrupting the DHFR (folate-related enzymes)	NR
Cladribine	Hairy cell leukemia	B-cell chronic lymphocytic leukemia, hairy cell leukemia	0.14 mg/kg for five days	100%	5.7-19.7 h	Disrupting the DNA synthesis of target cells	NR
Alemtuzumab	Chronic lymphocytic leukemia	Multiple sclerosis	30 mg/kg/three times a week	80%	10 h	Targeting the CD52 on the surface of the lymphocytes cell membrane	Phase II
Trastuzumab	HER2-positive breast cancer	Stomach cancer	600mg/every three weeks	87%	2.5 days	Induce apoptosis; Prevent ectodomain cleavage	Phase III

Table 2: Anti-cancer agents under self-administration for SC delivery.

Agent	Subcutaneous use for	Other diseases	Recommended dosing	Bioavailability	Half-life	Description	Clinical trial
Cytarabine (cytosine arabinoside)	Acute myelogenous leukemia	Leukemias, lymphomas	50 to 100 mg/m^2	109.8%	1.35h	Disrupting the DNA synthesis of target cells	NF
Azacitidine	Myelodysplastic syndromes	Myeloid leukemia, juvenile myelomonocytic leukemia	75 mg/m^2/day	89%	41 ± 8 min	Aberrant DNA hypermethylation	NF
Bortezomib	Myeloma; Mantle cell lymphoma	NR	3.5 mg	80%	40h	Disturbing the proteasome activity	Phase III
Omacetaxine	Chronic myelogenous leukemia	NR	1.25 mg/m^2/ day for 7.5 months	70-90%	7h	Disrupting the synthesis of protein.	NF
Bleomycin	Germ cell testicular cancer lymphomas	Hodgkin's lymphoma, non-Hodgkin's lymphoma, testicular cancer, ovarian cancer, cervical cancer	10-20 mg/m^2	70-100%	0.26 h	Cleaving the DNA of target cells	NF
Abagovomab	ovarian cancer	NR	2 mg/ml/day for two weeks	NF	NF	Targeting CA-125 in epithelial of cancer cell	Phase III

(Abrriviation: NF: Not Found, NR: Not Reported)

Subcutaneous delivery

Subcutaneous administration often involves a quick injection (a few seconds or minutes) into the hypodermis (under the skin). This route of administration is suitable for long-term therapies, offers an alternative for patients with poor venous access, reduces the risk of infectious complications, may be carried out in an outpatient setting, and enables educated individuals to self-administer. It needs less processing of pharmaceuticals and is more practical for patients and medical professionals. Overall, it might help the healthcare system spend less money [5,52-56]. In the section below, we discussed the chemotherapeutic agents that are administered through the SC route.

Methotrexate

One of the medications approved for self-administration in acute lymphoblastic leukemia [67-69]. Methotrexate (amethopterin) is well known as an anti-folate agent used in different

malignancies such as breast cancer, leukemia, lung cancer, lymphoma, gestational trophoblastic disease, and osteosarcoma [70-72]. Primarily the route for this chemotherapeutic agent is IV due to its need for high doses (more than 1g/m^2), while the oral route also is available for this agent but the absorption of it is not satisfactory. However, in the case of changing the delivery route of this agent, there is a need for intermittent low doses (20-30 mg) to bring effective outcomes. Due to the variable absorption, SC route for methotrexate is not common, while it is used in rheumatoid arthritis. The result of the study on five children who lived with acute lymphoblastic leukemia demonstrated that SC administration of 40 mg/m^2 of methotrexate can be completely absorbed the same as the IV. Due to the well-tolerated SC delivery of methotrexate in children, commercial syringes of prefilled methotrexate with a volume of 50 mg/ml are available [73-75].

Cladribine

Cladribine with the 2-chlorodeoxy-2'-adenosine formula is well known as an analog of purine used for patients with B-cell chronic lymphocytic leukemia and hairy cell leukemia [76,77]. Conventionally, this medication is used in IV routes 0.1 mg/kg/day for more than seven days and its prodrug needs to be phosphorylated in cancer cells to induce its cytotoxic effect [78,79]. However, cladribine is also one of the chemotherapeutic agents that the formulation for SC roots used 0.14 mg/kg for five days [80]. SC delivery of cladribine with a dosage of 0.14 mg/kg in 10 chronic lymphocytic leukemia patients demonstrated a bioavailability of 100%, concentration peak of 318 nM (for IV=169 nM), and half-life of 10 to13 h [81]. In the case of cladribine, the results of the SC delivery were satisfying the same as the IV [82].

Alemtuzumab

Alemtuzumab is widely used in the treatment of chronic lymphocytic leukemia and multiple sclerosis considered the first effort on SC administration of monoclonal antibodies [83-87]. This chemotherapeutic agent induces anticancer activity by targeting the glycoprotein antigen on the lymphocyte cell membrane called CD52 (also known as a CAMPATH-1 antigen) [88,89]. IV delivery is used as a primary route of alemtuzumab as a single medicine in the therapy of chronic lymphocytic leukemia with a dosage of 30 mg/kg (three times a week) for 12 weeks. Since this agent has long half-life (3 weeks), some research has been done to reschedule the administration program, and the SC route is used as an alternative [90]. Two different clinical trials of phase II on lymphocytic leukemia patients demonstrated that using the dosage of 30 mg/kg (3 times a week) in SC delivery leads to an overall response rate of 34% that was not comparable with the primary route (IV injection) of alemtuzumab [84, 88]. Self-administration of alemtuzumab by the patient is possible, but there is little data about the bioavailability of this drug in SC delivery [83, 88]. A study compared the serum concentrations of administration (dosage of 30 mg/kg/three times a week) in patients after IV and SC delivery that demonstrated the same results of maximal trough concentrations for both routes was 5.4 μg/ml. However, due to the slow absorption, there is a need for higher cumulative doses in SC delivery (551 mg, range=146-1106 mg versus 90 mg, range=13-316 mg) [91].

Trastuzumab

Trastuzumab is another monoclonal antibody that used SC routes as an alternative delivery manner [92,93]. This antineoplastic agent induces its anticancer effect by targeting the transmembrane receptor of Human Epidermal growth factor Receptor 2 (HER 2) on the surface of different tumor cells [94-99]. Moreover, trastuzumab can induce apoptosis in tumor cells and block ectodomain cleavage [100,101]. This agent has been approved for breast cancer therapy with overexpressing HER2 and the primary route for that is IV along with an adjusted two injections half an hour apart every three weeks [100,102-104]. Since patients need to receive trastuzumab for one year before and after surgery and due to the unsatisfactory response, SC delivery is considered a more convenient way. In the IV manner, trastuzumab is used at the dosage of 5- 30 ml every 3 weeks, while in the SC delivery of 120 mg/ml (600mg/every three weeks) of the drug used in each injection in combination with human hyaluronidase (10000 UI) to facilitates absorption. Intravenous trastuzumab infusion takes 90 minutes, which can be reduced to 30 minutes based on the patient's tolerance, while its subcutaneous injection usually takes less than 5 minutes and can be performed by the patient himself. Pharmacokinetics evidence confirms the efficacy and safety of trastuzumab 8 mg/kg and then 6 mg/kg/every 3 weeks for IV and 600 mg/ every 3 weeks for SC delivery before and after surgery that results in serum concentrations of 51.8 μg/ml and 69 μg/ml for IV and SC delivery, respectively. Evidence suggests that the SC delivery (12%) of trastuzumab reduces the adverse effect of the drug in comparison to the patients who received IV (21%) [95].

Cytarabine

Cytarabine is widely used as a therapy for leukemias and lymphomas [105]. This pyrimidine nucleoside cytidine analog for its activation needs to be phosphorylated within the cell and converted to the cytarabine triphosphate that gives its ability to block the DNA synthesis of cancerous cells. A wide range of dosages of this drug (from 100 mg to 6 g/m^2/day) is available for the treatment of malignancy [106]. SC delivery is used for low doses of cytarabine (50 to 100 mg/m^2) in patients with acute myelogenous leukemia instead of IV. The result of this study demonstrated the rapid absorption of cytarabine with a plasma peak of about 30min and bioavailability of 100% that was similar to the IV delivery. Now, this chemotherapeutic agent is used in the reduction phase of acute myelogenous leukemia through bolus injection of SC routes [107-109]. In addition, For pediatric patients with relapsed AML, cytarabine is an efficient induction regimen. In a study by Garg et al., they achieved 2-year EFS and OS rates of 29% (7%) and 34% (7%) at the initial relapse, with a complete remission rate of 66% [110].

Azacitidine

Azacitidine is widely used as a therapy for myelodysplastic syndrome, myeloid leukemia, and juvenile myelomonocytic leukemia [111-113]. This cytidine analog for its activation needs to convert to azacitidine triphosphate within the cell, which leads to reversing the aberrant DNA hypermethylation and then the reexpression of genes that are silenced [114,115]. Currently, SC delivery is available for a low dosage of azacitidine (75 mg/m^2/day) in some regions, while its administration through IV routes is also done in the USA [116]. However, SC delivery of more than 100 mg dosages needs an injection from two different sites. The plasma peak of azacitidine demonstrates rapid absorption within a 30min with a peak of 750 ng/ml for SC delivery and 2750 ng/ml after IV injections. However, there was a short shelf life after both routes, less than an hour with clearances of 2.5 l/min and a bioavailability of 89% [117]. The mean half-life in intravenous was roughly 22 min, whereas the mean half-life in subcutaneous was 41 min. The longer transition period needed for azaciti-

dine to transfer from the subcutaneous compartment into the circulation has been blamed for the longer mean half-life of the subcutaneous form. Another argument is that until azacitidine enters the plasma compartment, it is stable and bioavailable at the subcutaneous depot location. Maximum plasma concentration was seen at 0.5 hours after azacitidine was subcutaneously administered in all six subjects. Azacitidine and its metabolites are primarily excreted through the urine [116]. The blood's level of white blood cells may temporarily decline due to azacitidine, which raises the risk of contracting an infection. Additionally, it may reduce the quantity of platelets. Moreover, it can reduce the quantity of platelets, which are important for healthy blood coagulation and raise the risk of bleeding or infection. Storage of reconstituted and diluted abacavir for injection for intravenous delivery is permitted at 25°C (77°F), but administration must start within an hour. This medicine is not frequently utilized via the SC route due to the aforementioned difficulties and the likelihood of tissue sloughing because the drug is deposited close to the surface of the skin or mucosa [118,119].

Bortezomib

Bortezomib is widely used in the treatment of multiple myeloma and mantle cell lymphoma. This agent induces its anticancer activity by disturbing the proteasome activity [120-125]. IV injection were used as the primary route for bortezomib with a dosage of 1.3 mg/m^2/day, once every 4 days for 8 consecutive periods. Using the SC delivery of this agent in under phase III trials on 222 individuals who live with myeloma demonstrates an overall response rate of 42% [123]. However, individuals who received bortezomib through SC delivery had less peripheral neurotoxicity (38%) in comparison to the IV route (53%). The approved dosage of bortezomib for SC delivery is 1.3-1.5 mg/m^2 with a bioavailability of 100%, 72h after injection, and 30 min for plasma peak with a shelf-life of 65-95 h. Thigh and abdomen are the recommended sites for injection. In addition, some evidence suggests that using the SC delivery of bortezomib along with immunomodulatory agents can improve the convenience of therapy for patients [123,126,127].

Omacetaxine

Omacetaxine is not stated for self-administration. This semisynthetic form of homoharringtonine is used as an anticancer therapy for chronic myeloid leukemia [128-130]. This agent induces its anticancer activity by disrupting the synthesis of proteins. Since the IV administration of omacetaxine caused cardiovascularly adverse effects, thus SC delivery is used as an alternative route for this drug with a dosage of 1.25 mg/m^2/ day for 7.5 months [131,132]. Evidence suggest that omacetaxine has a plasma peak of 55 min and half-live of 7h with the bioavailability of 70-90% [133].

Bleomycin

Bleomycin is widely used as a therapy for Hodgkin's lymphoma, non-Hodgkin's lymphoma, testicular cancer, ovarian cancer, and cervical cancer. The primary route for this anticancer agent is IV, which then induces its activity by cleaving the DNA of target cells [106,134,135]. Subcutaneous delivery is through infusion also available for bleomycin. The bioavailability of this agent in SC delivery is 90%, 24h after injection [136,137].

Abagovomab

Abagovomab is another monoclonal antibody with a molecular weight of 165–175 kDa that is used in cancer therapy and now it is under-discussed for SC delivery [138,139]. CA-125 is an antigen target of this agent which has overexpression in epithelial ovarian cancer [140]. Abagovomab induces its anticancer activity by increasing the expression of IFN-γ and eliciting CD8+ and CD4+ T cells responses [141,142]. Phase III clinical trials has launched in MIMOSA on nine hundred women who had surgery to remove the ovarian tumor and are under chemotherapy. These patients received abagovomab from the SC route at a dosage of 2 mg/ml/day for two weeks, then followed one dose each month until 45 months [143,144]. A phase I/II clinical trial on patients with ovarian cancer demonstrated a 93.5% tolerance for SC delivery of abagovomab, which all received the monoclonal antibody for 4.9 months [142].

Daratumumab

Daratumumab is a monoclonal antibody used to treat cancer. It binds to CD38, which multiple myeloma cells overexpress. Adults whose prior therapy comprised a proteasome inhibitor and an immunomodulator are advised to consider daratumumab monotherapy as an option for treating relapsed and refractory multiple myeloma as a fourth line of treatment, that is, after 3 prior therapies. Administration Guidelines Over the course of three to five minutes, administer the daratumumab solution for subcutaneous injection into the subcutaneous tissue of the abdomen 7.5 cm to the right or left of the navel. As there are no data available, avoid administering daratumumab solution for subcutaneous injection at other body parts [145]. Anaphylactic reactions, among other severe and/or significant Infusion Related Reactions (IRR), can be brought on by daratumumab solution for subcutaneous injection. About 11% (52/490) of the individuals in clinical investigations had an IRR. Following the initial injection, Grade 1-2 IRRs predominated. About 11% (52/490) of the individuals in clinical investigations had an IRR. Following the initial injection, Grade 1-2 IRRs predominated. Less than 1% of patients experienced IRRs with successive doses [146,147].

Rituximab

Rituximab is a pharmaceutical used to treat specific types of vasculitis and rheumatoid arthritis that have not responded to other types of therapy. It functions by disabling a portion of the immune system that autoimmune illnesses cause to malfunction. After Cycle 8 (n=620) of the PrefMab Trial, which examined previously untreated DLBCL and follicular lymphoma, it was found that 77% of patients preferred subcutaneous RITUXAN HYCELA administration over rituximab IV administration since it needed less time in the clinic. Only the abdominal wall may receive subcutaneous injections of rituximab. Never administer medication to skin that is red, painful, hard, damaged, or covered in moles or scars. Give subcutaneously over roughly five minutes if you have non-Hodgkin's lymphoma [148,149]. Give subcutaneously over a period of around 7 minutes for CLL. Studies comparing the efficacy of subcutaneous (SC) and intravenous (IV) rituximab have found that both formulations are equally effective. However, most patients and medical professionals prefer the SC method due to its shorter chair time and lower risk of infusion-related complications. Recent Canadian data, including those from the scuba study described here, complement prior international studies' findings that the fixed SC dosing of the SC formulation reduces preparation and administration time, lowers the cost of administration, and reduces medication wastage. For the treatment of follicular lymphoma, diffuse large B cell lymphoma and chronic lymphocytic leukemia, the SC formulation is typically favored over the IV formulation because of the significant time and financial advantages [149].

Conclusion

Since the administration of anti-neoplastic agents through IV route faces some challenges like toxicity and postinjection infection, there is a need for finding new administration routes [150,151]. Therefore, SC delivery of chemotherapeutic agents has garnered more attention due to its high bioavailability (while trastuzumab and alemtuzumab are the exceptions), absorption, and being less invasive.

Like other routes, SC has also some challenges such as local toxicity, irritation, and necrosis in repeated SC injection. However, several technologies have been developed to overcome the limitations like the use of cyclodextrins and biochaperone, which are used along with chemotherapeutic agents in SC delivery to enhance their aqueous stability [152,153]. In some cases, nanoparticle technology is used and chemotherapeutic agents are loaded into the nanoparticles like hydrogels, nanoparticles, liposomes, and lipid prodrugs to improve the efficacy of SC delivery [154-161].

In comparison with the IV administration, there is no difference in the elimination rate of azacitidine, cladribine, bortezomib, and trastuzumab after SC delivery. As we mentioned, self-administration of SC routes is available in the case of methotrexate and cladribine, while in the case of omacetaxine, still there is a need for qualified health workers. In the case of omacetaxine, although there is an oral route, SC delivery is also available as an alternative in chronic myelogenous leukemia patients. SC delivery from the different sites has no effect on the absorption rate. As a whole, SC delivery of chemotherapeutic agents, in addition to its advantages for patients, has economic benefits in terms of healthcare and hospitalization costs. However, there is a need for further studies to establish the most suitable formulation of chemotherapeutic agents for SC delivery.

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