History of platinum-based drugs from a regulatory perspective

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Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

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AIDS	acquired immunodeficiency syndrome
AMIS	Arzneimittelinformationssystem
ANSM	Agence nationale de sécurité du médicament et des produits de santé
ASCO	American Society of Clinical Oncology
ATP7A	copper-transporting ATPase 1
ATP7B	copper-transporting ATPase 2
AUC	Area Under the Curve
BRCA1	breast cancer 1, early onset
BRCA2	breast cancer 2, early onset
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CMC	Chemistry, Manufacturing, and Control
CML	chronic myelogenous leukaemia
CTR1	copper transporter 1
CYP	cytochrome P450
DNA	deoxyribonucleic acid
DPPG	dipalmitoyl phosphatidylglycerol
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EMEA	Europe, the Middle East and Africa
EORTC	European Organization for Research and Treatment of Cancer
EPR	enhanced permeability and retention
FDA	Food and Drug Administration
FOLFOX	combination regimen with oxaliplatin, 5-fluorouracil and folinate
5-FU	5-fluorouracil
HMG	high mobility group
HR	hazard ratio

HRPC	hormone-refractory prostate cancer
ILS	increase in life span in treated over control animals
IND	Investigational New Drug
LD_{50}	median lethal dose, amount required to kill 50% of the test population
M-CAVI	methotrexate / carboplatin / vinblastine regimen
M-VAC	methotrexate / vinblastine/ doxorubicin / cisplatin regimen
M-VEC	methotrexate / vinblastine / epirubicin / cisplatin regimen
MMR	mismatch repair
NCI	National Cancer Institute
NCIC	National Cancer Institute of Canada
NCI RESIST	National Cancer Institute Response Evaluation Criteria in Solid Tumours
NDA	New Drug Application
NER	nucleotide excision repair
NSCLC	non-small cell lung cancer
OCT	organic cation transporter
ODAC	Oncologic Drugs Advisory Committee
p53	tumour suppressor 53
PARP	poly(ADP-ribosyl)ated proteins
PEG	polyethylene glycol
PFS	progression-free survival
PMDA	Pharmaceuticals and Medical Devices Agency
PVB	platinum / vinblastine / bleomycin regimen
SCLC	small cell lung cancer
SPARC	Satraplatin and Prednisolone Against Refractory Cancer
SPEAR	Study of Picoplatin Efficacy After Relapse
SWOG	Southwest Oncology Group
UK	United Kingdom
VAB	vinblastine / dactinomycin / bleomycin regimen

Introduction: platinum complexes as a cornerstone of chemotherapy of solid tumours

Three platinum complexes, cisplatin, carboplatin and oxaliplatin (Figure 1, Table 1 [1]), received a world-wide approval for treatment of several types of solid tumours. These inorganic compounds have revolutionised cancer chemotherapy and are now indispensable for oncologists. More than 40% of therapeutic regimens routinely applied in the clinic are platinum-based [1].

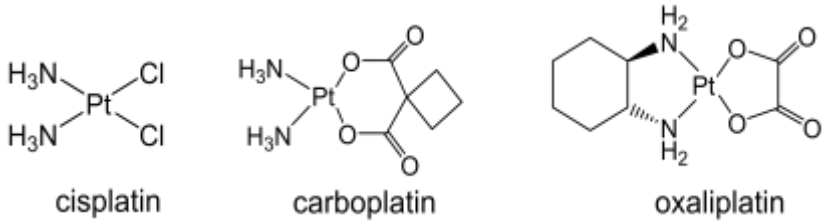

Figure 1. Chemical structures of the globally approved platinum drugs.

Table 1. Globally approved platinum-based drugs (modified from [1]).

Drug	Other names / brand names	Originator company	Dose-limiting toxicity
Cisplatin	Peyrone's chloride CDDP Platinol® Platidiam Platinex® Platistin Platosin Cisplatyl Platiblastin® Briplatin Abiplatin® Lederplatin Neoplatin Platibastin	Bristol-Myers	Nephrotoxicity
Carboplatin	JM8 CBDCA Paraplatin® Paraplatine Carboplat® Carbomedac® Carbosin Cycloplatin Ribocarbo	Bristol-Myers Squibb	Myelosuppression
Oxaliplatin	Eloxatin® Dacotin® Dacplat® Elplat®	Sanofi-Aventis	Neurotoxicity

Cisplatin is a gold standard in treatment of testicular, ovarian, bladder, lung, oesophageal, head and neck cancer, lymphomas and myelomas [1–3]. The cure rates are especially high in testicular cancer and exceed 90% if tumours are diagnosed at an early stage [2,4]. The approval of cisplatin by the Food and Drug Administration (FDA) in 1978 [5] and by other authorities later on led to a dramatic decrease in mortality of testicular cancer patients as Figure 2 illustrates. Cisplatin-based chemotherapy is accompanied by severe but manageable side effects, among them dose-limiting nephrotoxicity, cumulative peripheral neurotoxicity, irreversible ototoxicity finally resulting in hear loss, as well as nausea and vomiting [1,6]. Anti-emetic prophylaxis and intensive hydration before and after treatment are essential for the success of the therapy. Introduction of these measures were crucial to the clinical development of cisplatin [6] as discussed in detail below.

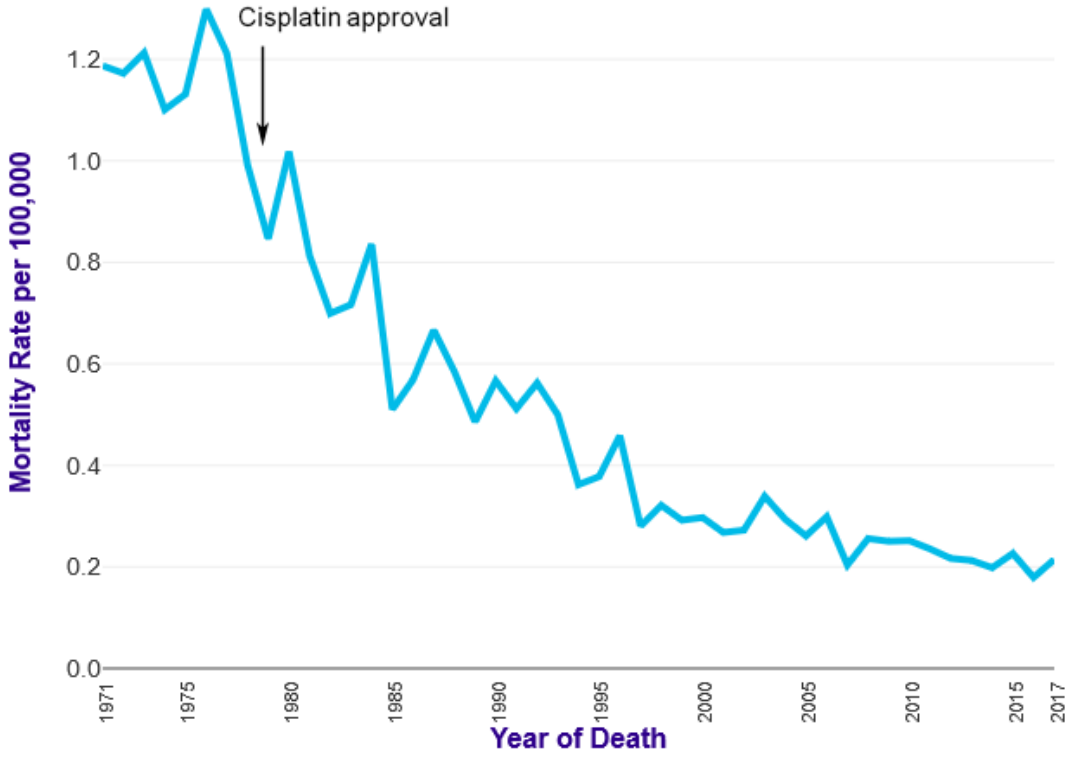

Figure 2. Age-standardised mortality rates, testicular cancer, UK, 1971-2008 (modified from [7]).

Carboplatin is distinguished by a much more favourable toxicity profile compared to cisplatin [3]. Due to the lower reactivity, carboplatin nephro- and ototoxicity are negligible [1,3,6]. For this reason, it is suitable for the aggressive high-dose therapy regimens [1]. The dose-limiting toxicity of carboplatin is myelosuppression, especially thrombocytopenia [4,6]. The main indication of the drug is ovarian cancer where carboplatin almost replaced cisplatin and is the first choice nowadays. In testicular cancer, the efficacy of carboplatin is rather limited; therefore, cisplatin remains a standard treatment of this disease. In other tumour entities such as bladder, non-small cell lung and head and neck cancer, the advantage of carboplatin over cisplatin has been a matter of debate, and for the lack of comparative studies cisplatin is still preferred [6].

As described in detail below, cisplatin and carboplatin produce the same active species, only with different kinetics. Their mechanism of action is thus principally the same, which leads to the similar therapeutic spectrum. For instance, both drugs are intrinsically inactive against colorectal cancer [2,6]. Oxaliplatin emerged to overcome this disadvantage. In the combination regimen

with 5-fluorouracil and folinate (FOLFOX), it is applied to efficiently treat metastatic colorectal cancer [1]. Oxaliplatin does not only exhibit distinct therapeutic activity, it also features a different side effect profile. The dose-limiting toxicity of the drug is peripheral sensory neuropathy [8].

Aim of this thesis

Platinum complexes have thus found their firm place in cancer treatment worldwide. Fifty years ago, however, nobody could ever think that these precious metal compounds would become precious in a different way, i.e. saving human lives [9]. The very idea of „putting a heavy metal into a person was an abomination" as Barnett Rosenberg who discovered the anticancer activity of platinum complexes put it [10]. In this thesis, the long and difficult path of the platinum drugs to worldwide approval is described from a regulatory point of view. This is followed by the review of locally approved platinum-based drugs.

The success of cisplatin, carboplatin and oxaliplatin has driven enormous efforts to develop new antitumour-active platinum complexes. Out of hundreds of novel compounds, several were evaluated in clinical trials, and for one drug candidate a New Drug Application (NDA) was filed at the FDA. However, they all failed to reach the market. In this thesis, obstacles in drug development and possible reasons for abandoning the most promising candidates are analysed. Finally, current developments and outlook depict the likely future of this fascinating class of anticancer drugs.

Serendipitous discovery of the cytostatic activity of cisplatin

Cisplatin (cis-diamminedichloridoplatinum(II)) was first prepared in 1845 by the Italian chemist Michele Peyrone and was known since then as Peyrone's chloride. This complex played a decisive role in the establishment of coordination chemistry theory by Alfred Werner, who received a Noble Prize in 1913 [2]. Interestingly, Barnett Rosenberg (1926 – 2009, Figure 3), the man responsible for the revival of cisplatin, did not even aim at working with the platinum compound [6].

Figure 3. Barnett Rosenberg (as in [6]).

Rosenberg joined the newly founded Biophysics department at Michigan State University in 1961. Inspired by the resemblance of iron filings clinging to a bar magnet to the appearance of condensed chromosomes in a cell during mitosis [4,11], he studied effects of alternating currents of different frequencies on cellular division in 1965 [12]. For this purpose, Rosenberg's team started with the common bacterium *Escherichia coli* to set the experimental parameters prior to work with mammalian cells [4,11]. The culture chamber included a pair of platinum electrodes to generate electricity as platinum was known to be inert in a biological environment. Rosenberg and colleagues turned on the electric field after bacterial population had reached steady state and observed a decrease in the density of bacteria. What was even more striking, bacterial rods grew into long filaments (Figure 4), up to 300 times longer than normal [4,6].

Figure 4. Normal (left) and filamentous (right) forms of *Escherichia coli* (as in [6]).

It was clear to Rosenberg that the electric field was not alone responsible for the observed phenomenon. He engaged a chemist, Thomas Krigas, who identified ammonium hexachloridoplatinate $(NH_4)_2[PtCl_6]$ in the culture medium of the chamber. This complex did indeed have antibacterial activity but, strangely enough, could not induce filamentation [4]. However, Loretta Van Camp observed that after a prolonged storage of the solution, it produced some short filaments [4,6]. That brought the researchers to the idea that light played a pivotal role. In further experiments, they found cis-diamminetetrachloridoplatinate(IV) (Figure 5) as a key compound that stopped bacterial cell division but not cell growth. Interestingly, the trans-

configured isomer (Figure 5) had no activity at all. Rosenberg and co-workers also prepared the counterparts featuring Pt(II), cisplatin and transplatin (Figure 5). Of the latter two compounds, only cisplatin, already known for more than a century as Peyrone's chloride, possessed the desired activity. Rosenberg's experimental setup involved two pieces of fortune: the use of presumably inert platinum electrodes and presence of ammonium chloride in the culture medium. But as Louis Pasteur once said, „in the field of observation, chance favours only the prepared mind" [13]. It had taken the researchers two years of determined work before their efforts were crowned with success [6].

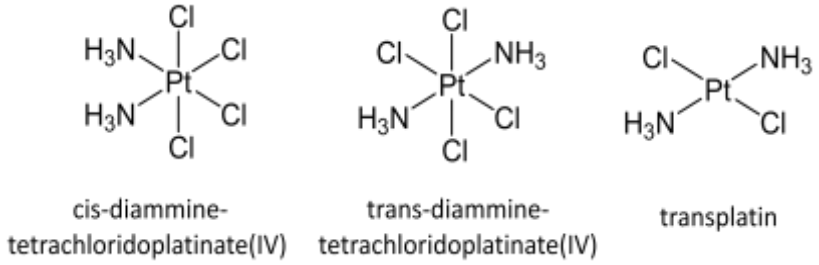

Figure 5. Chemical structures of transplatin, cis- and trans-diamminetetrachloridoplatinate(IV).

Rosenberg's team proceeded with cisplatin and the Pt(IV) counterpart cis-$[Pt(NH_3)_2Cl_4]$. They hypothesised that since the compounds halted cell division in bacteria without signs of toxicity, it may stop cell division in rapidly growing tumours without damaging the whole body [4,9]. Having determined the safe dose levels to be administered to mice (8 mg/kg of animal body weight being non-lethal with LD_{50} of 13 mg/kg), researchers implanted a piece of malignant tumour, the solid Sarcoma-180, into experimental animals. After treatment of progressing tumours with cisplatin at the dose of 10 mg/kg, the tumour weight was measured and compared to the initial value. The reduction of tumour weight by more than 50 % was considered efficient. Already in first experiments, cisplatin showed activity far beyond that. All subsequent tests confirmed the astonishing results. Cisplatin appeared to be the most potent of the tested compounds, able to regress large Sarcoma-180 tumours (about 1 g tumour in a 20 g mouse) as illustrated in Figure 6 and to completely cure animals [4].

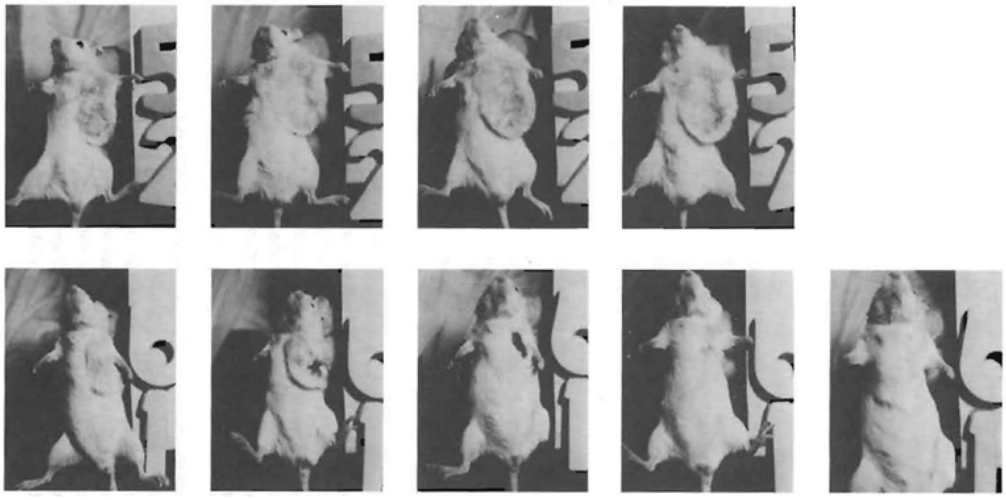

Figure 6. Time sequence photographs of study animals with solid Sarcoma-180 tumours: an untreated negative control mouse (upper panel) and a mouse treated with cisplatin (as in [4]).

Rosenberg contacted Gordon Zubrod, the head of the chemotherapy branch of the National Cancer Institute (NCI) for further evaluation. He was invited to introduce his new compounds at the NCI. There was not much enthusiasm among cancer researchers about the heavy metal drug candidates; however, NCI agreed to test the complexes on L1210 leukaemia in mice. The results were very promising also in this model. Rosenberg submitted a grant application to the NCI and received funding to support further development of cisplatin. A short communication describing the findings was published in Nature [14]. Noteworthy, another renowned American journal rejected the manuscript as a reviewer had commented that there were so many drug candidates around and another one did not deserve attention [4]. But when Professor Sir Alexander Haddow, the head of the Chester Beatty Institute in London, who intuitively anticipated the coming success of cisplatin, confirmed compound activity against myeloma in mice, more and more researchers started to take notice [4,11]. Interestingly, back in 1966 Rosenberg's colleague sent some cisplatin a friend to evaluate the anticancer activity. But his friend overdosed the animals, which all died, and reported back that the drug was too toxic. Such an irony of fate!

Cisplatin was subsequently tested in a wide variety of tumours, but mostly in small groups of animals making any statistical analysis meaningless. The best results are presented in Table 2 and can be summarised as follows [4]:

- cisplatin showed marked antitumour activity, and in some tumour types it was potent enough to save animals a few days before death;
- cisplatin had a broad spectrum of activity;
- the drug exhibited no animal specificity.

Table 2. Best results of the antitumour activity of cisplatin in animal models (modified from [4]).

Tumour	Host	Results
Sarcoma-180 solid advanced	Swiss white mice	100 % cures
Sarcoma-180 ascites	Swiss white mice	100 % cures
Leukaemia L1210	BDF_1 mice	% ILS = 379 %, 4 / 10 cures
Primary Lewis lung carcinoma	BDF_1 mice	100 % inhibition
Ehrlich ascites	BALB/c mice	% ILS = 379 %
Walker 256 carcino-sarcoma	Fisher 344 rats	100 % cures
Dunning leukaemia	Fisher 344 rats	100 % cures
P388 lymphocytic leukaemia	BDF_1 mice	% ILS = 533 %, 6 / 10 cures
Reticulum cell sarcoma	C+ mice	% ILS = 141 %
B-16 melano-carcinoma	BDF_1 mice	% ILS = 279 %, 8 / 10 cures
ADJ/PC6	BALB/c mice	100 % cures
AK leukaemia (lymphoma)	AKR/LW mice	% ILS = 225 %, 3 / 10 cures
Ependymoblastoma	C57BL/6 mice	% ILS = 141 %, 1 / 6 cures
Rous sarcoma advanced	15-1 chicken	65 % cures
DMBA-induced mammary carcinoma	Sprague Dawley rats	77 % total regression, 3 / 9 tumour-free

ILS = increase in life span in treated over control animals

Cisplatin was not always superior to the antitumour drugs established at that time like nitrogen mustard and other alkylating agents but luckily, the importance of toxicity issues raised in the

1960s due to development of combination regimens. Therefore, many clinicians were ready to develop eventually less potent compounds, if they showed little or different toxicity to the healthy tissue. Only a minor effect of cisplatin on bone marrow advantageously contrasted the toxicity spectrum of the available antitumour drugs and ensured its entry into the next stage of drug development [9].

How do platinum drugs work?

Drug development cannot be properly understood without having an idea about its (bio)chemistry and pharmacology. For this reason, this chapter will briefly describe the current view of cisplatin mechanism of action that is schematically depicted in Figure 7.

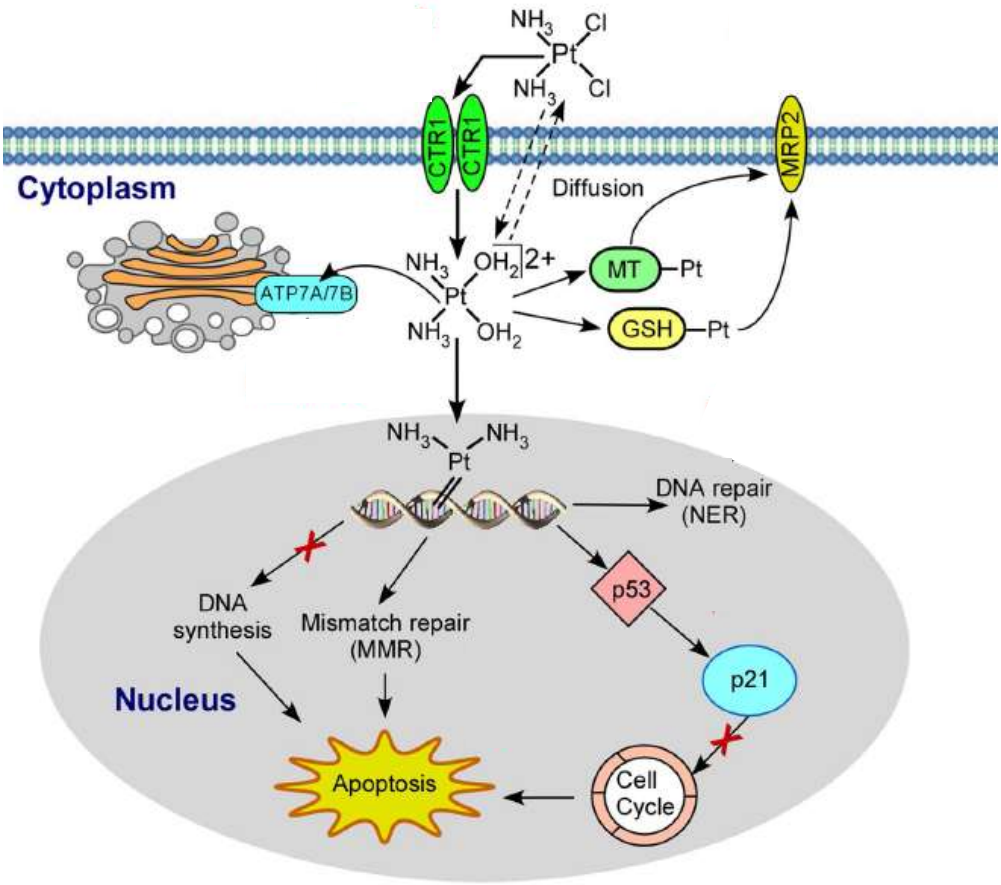

Figure 7. Schematic representation of the mechanism of action of cisplatin (modified from [3]).

Given its concentration-dependent and unsaturable uptake, cisplatin had been long assumed to enter the cell solely via passive diffusion. However, intensive studies of the last decade clearly indicated the contribution of several transport proteins to the cellular accumulation of the drug. The role of copper transporter 1 (CTR1) in cisplatin uptake is especially well documented as downregulation of this protein is often observed in cisplatin-resistant cells and low expression of CTR1 correlated with poor response to the drug in lung cancer patients [15,16]. Other copper transporters, namely copper-extruding P-type ATPases ATP7A and ATP7B, were implicated in cisplatin transport as they were reported to be upregulated in resistant cell lines [17]. Moreover, high expression of these transporters was associated with decreased overall survival [16,18]. Other transporters like Na^+,K^+-ATPase and volume-regulated anion channels were implicated in cellular uptake of cisplatin, too [3].

Inside the cell with much lower chloride concentration (4 – 20 mM) than in the blood stream (ca. 100 mM), cisplatin undergoes hydrolysis yielding mono aqua and diaqua species [1]. These reactive complexes readily bind to cytoplasmic peptides (e.g. glutathione) and proteins. On one

hand, it lowers the concentration of active platinum species, and elevated glutathione levels were associated cisplatin resistance in cell line models [19]. On the other hand, binding to glutathione and other antioxidants shifts the cellular redox status leading to oxidative stress. This process plays an important role in cisplatin side effects such as nephrotoxicity [20]. As described in more detail below, the aquation rate of carboplatin is much lower due to the cyclic structure formed by the bidentate cyclobutane dicarboxylate leaving group. The reduced reactivity of carboplatin accounts for a much more favourable toxicity profile. It should, however, be noted that the reactive species formed by the hydrolysis of cisplatin and carboplatin are the same, while oxaliplatin produces a different diaqua complex. The hydrolysis rate of oxaliplatin is higher as compared to carboplatin but much lower than in the case of cisplatin limiting side effects to peripheral sensory neuropathy.

In the case of all three drugs, the reactive platinum species interact with DNA, in particular with N7 atoms of guanine and adenine residues. They form intrastrand and interstrand adducts, of which the intrastrand crosslinks between adjacent guanine bases appear to be pivotal for the cytotoxic effect [3]. This DNA lesion induces a significant distortion of the double helix [21]. The kink is subsequently recognised by several cellular proteins such as non-histone chromosomal high mobility group (HMG), nucleotide excision repair (NER) and mismatch repair (MMR) proteins [3]. HMG proteins recognise Pt-DNA crosslinks between adjacent guanines inducing alterations in the cell cycle and finally apoptosis [22]. They also shield platinum adducts from repair [23]. In contrast, NER system is employed to remove platinum adducts and to repair DNA damage [3]. MMR protein complex tries to repair the base mismatch it recognises but due to the presence of bound platinum the repair fails finally initiating apoptosis [3]. Since cisplatin and carboplatin yield the same active species, these drugs form the same DNA adducts. As also specified below, oxaliplatin possesses a bulky lipophilic 1,2-diaminocyclohexane ligand and therefore, induces a different conformational distortion on DNA. Oxaliplatin-DNA adducts are processed differently to those of cisplatin, e.g. they are not recognised by the MMR system. This makes oxaliplatin antitumour action MMR-independent and accounts for the different activity profile compared to the other two platinum drugs. Recently, another protein family, poly(ADP-ribosyl)ated proteins (PAPR), crucial for base excision repair, has attracted attention because of their high expression and hyperactivity in cisplatin-resistant cells [24]. High mobility group proteins facilitate the binding of tumour suppressor p53 to DNA-activating genes, which are involved in cell cycle control, DNA repair and apoptosis. p53 mutations correlate with lower survival of ovarian cancer patients [25]. Due to the low incidence of mutated p53, testicular tumours are particularly sensitive to cisplatin [26]. Especially efficacy of the platinum drug against testicular cancer was central to its clinical success and to the regulatory approval.

Clinical development of cisplatin

In 1970, cisplatin entered clinical trials. The drug was studied in patients who did not benefit from other treatments [11]. A Phase I study was accompanied by the occurrence of severe renal damage at 40 mg cisplatin/m^2 (related to body surface area), omnipresent emesis and sporadic ototoxicity [6]. Severe nausea and vomiting were observed already at the dose of 5 to 10 mg/m^2, and the defined dose schedule implied 100 mg/m^2. The extent of acute emesis was so high that people refused to take medication. However, kidney toxicity was of utmost concern for all clinicians [9]. Phase I studies do not aim at assessing efficacy, however, with cisplatin promising response was observed in testicular and ovarian tumours [9,27]. In one of the pilot studies carried out at the Roswell Park Memorial Institute, response was seen in 13 out of 15 patients with testicular cancer, seven of them experienced complete remission for at least one month or longer [28]. Nevertheless, the encountered degree of nephrotoxicity was considered unacceptable. Fortunately, Cvitkovic and colleagues could show first in animal model [29] and then in patients [30] that aggressive hydration with saline supported by osmotic diuresis with mannitol could prevent renal failure even at increased dose. This technique, which is standard in cisplatin-based chemotherapy nowadays, literally saved the development of the drug. In the 1970s, anti-emetic medication applied to relieve cisplatin-induced nausea and vomiting consisted of phenothiazines and subsequently metoclopramide [31]. Only after 1990, the discovery of 5-HT_3-receptor antagonists like ondansetron and granisetron allowed taking full control over emesis of cisplatin-treated patients [32].

Phase II clinical trials started in 1975 after finding a way to alleviate nephrotoxicity [9]. By then, understanding that tumour remission is facilitated through exposure to a combination of drugs had developed in the scientific community. It was already known that high doses of vinblastine and bleomycin produced good responses in 75 % of patients with testicular cancer [33]. However, due to high toxicity a great proportion of young men died from treatment. Through incorporation of cisplatin into this regimen, toxic side effects could be significantly reduced and efficacy greatly improved. In the first trial of the PVB (platinum, vinblastine, and bleomycin) schedule, 35 out of 47 patients, i.e. 74 %, experienced complete remission, and the rest showed partial response. With five patients becoming tumour-free after subsequent surgery, the overall disease-free status of 85 % was achieved. Most of these men were long-term survivors [4]. In another trial at the Memorial Sloan Kettering, the addition of cisplatin to the VAB regimen (vinblastine, dactinomycin, and bleomycin) enhanced the percentage of complete responses from 14 to 50 %, with an appreciable proportion of 24 % long-term survivors [34]. In testicular cancer, long-term survival actually means cure because fast tumour growth allows early detection of relapse. This was a great success given that before cisplatin entered the stage of cancer therapy, germ cell tumours of testes were almost always lethal [27] and only 5 % of patients expected to be cured compared to over 90 % today [4].

While in 1970s testicular cancer was one of the most fatal male diseases, women suffered and died from ovarian cancer in great numbers. Prior to cisplatin discovery, patients with advanced disease were treated with alkylating agents and doxorubicin. Remission was observed in up to 60 % cases, with no more than 5 % surviving longer than five years [4]. In the starting Phase II trial with cisplatin, response was seen in 7 of 25 women (28 %) with adenocarcinoma of ovary [4]. In subsequent studies with single-agent cisplatin in patients who failed previous chemotherapy, around 30 % experienced tumour remission. As first-line treatment, cisplatin led to response in

60 % of cases, and for 30% of patients complete regression was reported [9]. If one compared only the response rates, cisplatin did not offer any advantage over the existing therapy, but the proportion of complete regression was impressive. Complete regression enabled surgical interference in previously inoperable cases of advanced ovarian cancer, which concerned a large proportion of women with this disease. Although due to frequent development of resistance and tumour relapse the complete cures were rather rare, overall survival was significantly improved by cisplatin.

The new platinum drug had a huge impact on therapy of advanced bladder cancer, too. In a Phase II trial, several regimens for treatment of this disease were compared. The response rates for cisplatin as a single agent were with 35 % not impressive; however, the drug greatly outperformed other chemotherapeutics such as adriamycin alone or in combination with other drugs. When given together with cyclophosphamide, the response increased to 61 % [35].

These convincing results urged Bristol-Myers Co Ltd., which formulated the final drug product, to file an approval application at the FDA in 1978. The formulation contained sodium chloride and mannitol, so that reconstitution with water would yield an isotonic solution [9]. The addition of sodium chloride was supposed to prevent hydrolysis at the time of storage. The drug product was named Platinol®. The submission NDA018057 was classified as Type 1 - New molecular entity [5]. Unfortunately, the original review and label are not available, but there is evidence that the pilot study in testicular cancer at the Roswell Park Memorial Institute mentioned above was decisive for the positive opinion of the FDA [11]. Platinol® received approval on December 19, 1978 [5]. Since then, a number of variations mostly concerning manufacturing have been submitted. Two variations on efficacy were submitted in 1981 and 1993, the latter one concerned new dosing regimen. No information on the content of this variation is, however, freely available. Interestingly, the current label does not contain any information on dosing. It should be noted that throughout the history indications on the label stayed the same, also after the development and marketing authorisation of generic products [5].

In some European countries, the indication spectrum was wider than in the United States. It is, however, uncertain when the label included other tumour entities than those specified above. Below, a short overview of the early trials in other tumour types is given. The information, which of these studies provided the basis for regulatory approval, is unfortunately not available from open sources.

First trials in non-small cell lung cancer (NSCLC) started in the late 1970s and all showed an adverse effect profile expected for cisplatin. Phase II studies of cisplatin in combination with etoposide [36] or vindesine [37] or cyclophosphamide / doxorubicin [38] or mitomycin C / vinblastine [4] showed response rates of above 30 %. The latter combination appeared to have the highest response rate, however, no regimen led to a clearly longer survival [4]. Nevertheless, a meta-analysis conducted by the NSCLC collaborative group revealed that platinum-based chemotherapy offered a small but significant survival advantage over other therapeutic options. In a large study in 1990s with 512 patients, significantly improved survival was observed in patients treated with high-dose cisplatin and vinorelbine as compared to single-agent vinorelbine and cisplatin / vindesine [39] making the former regimen standard of care for patients with advanced NSCLC [4]. In small cell lung cancer (SCLC), cisplatin / etoposide combination demonstrated response rates of 60-80 % in previously untreated patients [4]. However, this

regimen had no advantage over the standard cyclophosphamide / doxorubicin / vincristine. Nevertheless, the combination of cisplatin and etoposide was favoured in refractory patients [4].

In head and neck squamous cell carcinoma, cisplatin combination with 5-fluorouracil was superior to other combinations and single-agent regimens in terms of response rates but failed to improve survival [4]. Cisplatin-based chemoradiotherapy appeared more promising. A trial in 157 patients demonstrated significantly longer 5-year survival ($p<0.02$) of 24 % upon cisplatin / 5-fluorouracil and radiation compared to 10 % on radiation alone [40]. This regimen is still standard therapy of head and neck cancer nowadays [41].

In cervical cancer, cisplatin was first evaluated as single-agent therapy and demonstrated response rates up to 30 %, with almost 1/3 of patients being complete responders [42]. In combination with isosfamide in a Phase II trial, the overall response rate of 50 % could be achieved, and the regimen was acceptably tolerated. Interestingly, 70 months after the end of the therapy 11 patients (37 %) were still alive [43]. In a triple combination with bleomycin, 69 % objective responses were seen, 20% being complete responses. Most common side effects were well-manageable nausea and vomiting [44]. It should, however, be noted that these studies date back to late 1980s – early 1990s and their relevance for regulatory approval of cisplatin is unclear. Later, combination with paclitaxel became the most favoured by oncologists [4,45].

Cisplatin was approved in the United Kingdom (UK) in March 1979 [9]. The earliest approved product listed on the website of the British Medicines and Healthcare products regulatory agency is, however, the generic Cisplatin Hospira, which received marketing authorisation on September 6, 1996. Interestingly, the approved indication spectrum was wider than that authorised by FDA. In addition to the above mentioned advanced or metastatic testicular, ovarian and bladder cancer, it included non-small and small cell lung carcinoma, squamous cell carcinoma of the head and neck, and also cervical carcinoma when combined with chemo- or radiotherapy [46]. A marketing authorisation application for the drug product called Platinex® from Bristol Arzneimittel GmbH was submitted to the German Federal Institute for Drugs and Medical Devices on July 12, 1978 and was approved on May 25, 1979 for treatment of testicular, ovarian and bladder cancer [47]. The marketing authorisation for cisplatin in France was granted to Sanofi Aventis on April 23, 1979 in a national procedure. The product was, however, discontinued on November 17, 2011. The oldest French approval still valid is that for the generic product of TEVA SANTE dating back to August 24, 1998. Unfortunately, no labelling is available on the website of the national competent authority ANSM, so that no conclusion on the approved indication can be drawn [48]. The earliest approval in Austria listed on the website of the Austrian Medicines and Medical Devices Agency is of November 10, 1987, and also likely represents a generic drug. The indication spectrum is the same as mentioned above for Cisplatin Hospira approved in the UK [49].

Carboplatin: development and approval history

The success of cisplatin stimulated search for other platinum complexes, which would be as active as cisplatin but exhibit less adverse effects. At that time, it was already known that active platinum species are formed upon substitution of chloride ligands with water molecules. Scientists correctly assumed that the toxic side effects arise from the very same species as the antitumour action. Therefore, researchers at the Institute for Cancer Research in London in collaboration with Johnson Matthey and Bristol-Myers Squibb evaluated several analogues with different amine ligands and various leaving groups. Toxicity was investigated in Wistar rats and activity was assessed in tumours grown in immune-deprived mice. Of eight extensively studied compounds, only carboplatin (JM8, diammine(1,1'-cyclobutanedicarboxylatoplatinum(II)) combined promising anticancer activity with a favourable toxicity profile [50].

Subsequent Phase I studies indeed indicated more tolerable toxicity as compared to cisplatin. This allowed the increase of the dose up to 400 mg/m^2. The side effect spectrum was also different. Nephrotoxicity and ototoxicity events were rare, and the dose-limiting toxicity was myelosuppression, with thrombocytopenia being the most pronounced. Already then, it was evident that the severity of myelosuppression correlated with renal function and previous treatment. The following Phase II trials showed some responses in advanced ovarian cancer patients who failed prior therapy with alkylating agents, radiation and even cisplatin-based regimen. Although response rates were modest, this observation warranted further evaluation of carboplatin [51]. In a Phase III study in patients with stage III and IV ovarian cancer at the Royal Marsden Hospital, carboplatin was compared to cisplatin. The response rates were 65.4 % in the carboplatin arm and 68.4 % in the cisplatin arm. With respect to neuro- and ototoxicity as well as renal failure, cisplatin proved to be much more toxic. Only myelosuppression was higher on carboplatin. From 21 patients who failed cisplatin therapy, four partial responses were seen in the 2nd line carboplatin treatment [52]. It may appear controversial to the pre-clinical findings and to the mechanism of action described above. However, the reasons for partial response to the 2nd line carboplatin were not analysed in that study. If in these patients cisplatin was discontinued due to toxicity, then their sensitivity to carboplatin was not surprising. The relationship between cisplatin and carboplatin dose (e.g. low cisplatin dose and high carboplatin dose) may have played a role, too [53]. Nowadays, it is known that some relapsed patients have so-called platinum-sensitive recurrence. Clinically, these are patients who experience disease recurrence later than six months after the first therapy. This enigmatic phenomenon has been attributed to the putative cancer stem cells and / or cells associated with the components of the extracellular matrix, which remain after the 1st line therapy and ensure the appearance of new platinum-sensitive tumour cells [54].

Predictable pharmacology facilitated the development of a simple dosing scheme for carboplatin, the Calvert formula. Egorin et al. found that the extent of thrombocytopenia depended on the free platinum exposure (area under the curve, AUC), and the latter was determined by the dose and the glomerular filtration rate. This observation was made already in Phase I studies. Subsequently, Calvert and colleagues derived a formula to calculate the dose based on the target AUC and renal function [55].

The drug product called Paraplatin®, developed by Bristol-Myers Squibb, was approved by the FDA with "1B" rating (moderate therapeutic advantage over existing therapies) on March 3, 1989.

The Oncologic Drugs Advisory Committee recommended it for approval on December 19, 1988. The indication included at that time only 2nd line treatment of advanced ovarian cancer. This was not due to exceptional efficacy of carboplatin in relapsed patients but rather seen as a chance for refractory patients to receive chemotherapy with a tolerable safety profile [56]. The FDA specified that mature comparative survival data of cisplatin vs. carboplatin would be needed to approve Paraplatin® as a 1st line therapy. In 1991, the company submitted the first-line use application based on two randomised controlled studies comparing cisplatin and carboplatin therapy, both in combination with cyclophosphamide, in 800 ovarian cancer patients. The results of these trials conducted by the National Cancer Institute of Canada (NCIC) and the Southwest Oncology Group (SWOG) showed equivalent overall survival and equivalent time to progression in both groups [56,57]. In the SWOG study, clinical response was 52 % in the cisplatin arm and 61 % on carboplatin [58]. Clinical response of 57 % and 59 % and overall survival of 100 and 110 weeks were found in cisplatin and carboplatin arms of the NCIC trial, respectively [59]. The toxicity pattern differed significantly between the cisplatin- and carboplatin-containing regimens. Non-haematological adverse events such as nephrotoxicity, neuromuscular toxicity and emesis were much more frequent and pronounced upon cisplatin treatment ($p \leq 0.001$ for all toxicities in the SWOG trial). Carboplatin induced significantly more thrombocytopenia ($p<0.001$), which is its dose-limiting toxicity as mentioned above. Interestingly, when Bristol-Myers Squibb introduced paclitaxel for ovarian cancer treatment, physicians noticed that combination with this taxane facilitated recovery from carboplatin-related haematological toxicities [60].

The oldest label available on the FDA website is from 2003 when the new dosage form was approved. Paraplatin® was then indicated for initial treatment of advanced ovarian carcinoma and the palliative treatment of ovarian cancer patients relapsed after prior chemotherapy including those who received cisplatin. The label highlights the application of Paraplatin® in combination with other chemotherapeutics, specifically with cyclophosphamide [57].

Most early trials in small cell lung cancer were performed at the Royal Marsden Hospital. In one of the studies in untreated patients with extensive disease, a response rate of 67 % was achieved indicating that carboplatin could be a promising approach for this tumour entity. The most effective therapy at that time was etoposide, which was able to induce complete or partial response only in 45 % untreated patients [51].

In head-and-neck cancer, the Southwest Oncology Group evaluated cisplatin / 5-fluorouracil (5-FU) combination and carboplatin / 5-fluorouracil vs. methotrexate in 261 patients. The overall response rate was significantly better on cisplatin (32 %, $p<0.001$) and improved with carboplatin (21 %, $p=0.05$) as compared to methotrexate (10 %). Whereas the toxicity of cisplatin regimen was significantly more pronounced than on methotrexate ($p=0.001$), carboplatin / 5-fluorouracil toxicity was intermediate [61]. Another trial was terminated since the control arm with cisplatin proved significantly better than the carboplatin arm in terms of response at the interim analysis ($p=0.04$). Carboplatin regimen showed greater haematological toxicity ($p<0.01$) but vomiting predominated in the cisplatin / 5-FU arm (<0.001) [62]. Taken together, only toxicity profile was somewhat more favourable for carboplatin. Therefore, cisplatin was still preferred in the carcinoma of head and neck, but carboplatin became more advantageous if the adverse effects were of concern. This is also reflected in the indications approved in some European countries later.

In 1990s, only small trials were conducted in metastatic or recurrent cervical cancer, and modest response upon carboplatin treatment was observed. In one Phase II trial with carboplatin in combination with etoposide, the response rate was 12.5 % [63] and in another, with single-agent carboplatin, response was seen in 15 % of patients [64]. It is unclear, which data provided the basis for approval of carboplatin in this indication in European countries. Only recently, results of a randomized Phase III trial of cisplatin / paclitaxel vs. carboplatin / paclitaxel in stage IVb persistent or recurrent cervical cancer have been reported. Both regimens were comparable in terms of overall survival (18.3 months for cisplatin- vs. 17.5 months for carboplatin-based combination). However, the percentage of non-hospitalisation days was significantly lower in the carboplatin arm ($p<0.001$) [65].

One early Phase II trial in bladder cancer studied carboplatin in combination with methotrexate and vinblastine. The response rate was rather high (48 %) and the side effects moderate [66]. One of the subsequent Phase II studies compared M-VEC treatment (methotrexate, vinblastine, epirubicin, and cisplatin) with the similar carboplatin-based regimen and found higher overall clinical response rate in the cisplatin arm (71 %) than in the carboplatin arm (41 %). Nevertheless, gastrointestinal side effects ($p=0.04$), nephrotoxicity ($p=0.03$) and neurotoxicity were significantly less pronounced during carboplatin treatment as compared to cisplatin. Leucopenia and neutropenia were worse but the difference was not statistically significant ($p=0.4$) [67]. In another trial comparing M-CAVI (methotrexate, carboplatin, and vinblastine) with the cisplatin-based M-VAC (methotrexate, vinblastine, doxorubicin, and cisplatin) did not reveal significant differences in efficacy between the two arms (overall response rates were 39 % for M-CAVI and 52 % for M-VAC, $p=0.3$). Also in this study, less adverse effects were seen upon carboplatin treatment [68].

As non-small cell lung cancer is concerned, the two platinum drugs were found to have comparable efficacy. In one EORTC (European Organisation for Research and Treatment of Cancer) trial with 288 patients, cisplatin in combination with etoposide induced 27 % objective responses comparing to 16 % on carboplatin but the difference was not statistically significant ($p=0.07$). There was also no significant difference in survival [69]. In another trial with 109 patients, similar results were obtained (23 % and 22 % response rate, respectively) [70]. In these studies, carboplatin-based regimen had less side effects than cisplatin treatment [69,70], which was in agreement with the findings in other tumour entities. Such results justified the approval of carboplatin for treatment of non-small cell lung cancer in some countries.

The submission for the product Carboplat® was done in Germany by Bristol Arzneimittel on July 3, 1986. The drug received approval on June 3, 1988. The indication spectrum provided in the AMIS (Arzneimittelinformationssystem) database is as of March 28, 2006 and mentions epithelial ovarian cancer, small cell lung carcinoma, squamous carcinoma of the head and neck, and metastatic or recurrent cervical cancer [47]. In the UK, carboplatin was authorised on July 20, 1990 for treatment of ovarian carcinoma of epithelial origin and of small cell lung carcinoma. Also here we can see that the indication spectrum is wider than the one approved by FDA [71]. The approval in France for Pfizer Holding was available on July 24, 1992 [72]. In Austria, the drug was authorised through the national procedure on August 9, 1995 with the same indication as in the UK but with the following extension. As an alternative to cisplatin in the cases cisplatin cannot be used, carboplatin indication included bladder cancer, squamous carcinoma of the head and neck, non-small cell lung cancer and cervical carcinoma [49].

Oxaliplatin: a breakthrough in colorectal cancer

Already in the early screening of novel compounds performed by the Institute of Cancer Research and Johnson Matthey, which resulted in identification of carboplatin as a promising compound, it was evident that introduction of other amine ligands, especially 1,2-diaminocyclohexane, may help to overcome cisplatin resistance [50]. Oxaliplatin ((1R,2R-diaminocyclohexane)-oxalatoplatinum(II)) was first synthesised in Japan by Kidani and co-workers [6]. They experimented with different isomers of 1,2-diaminocyclohexane and found that (cis-1,2-diaminocyclohexane)oxalatoplatinum(II) had a higher therapeutic index in ascites Sarcoma-180 than other compounds [73]. It combined a relatively low reactivity due to the bidentate leaving group with a more lipophilic carrier ligand as compared to cisplatin. This higher lipophilicity may account for different uptake mechanisms. As mentioned above, cisplatin employs passive diffusion and active transport via CTR1, Na^+,K^+-ATPase and volume-regulated anion channels to enter the cells. Oxaliplatin uptake appears to rely more on organic cation transporters OCT1 and OCT2. Overexpression of these transporters was reported to increase cellular accumulation of the drug. Moreover, OCTs are abundantly present on the surface of colorectal cancer cells, which may explain high sensitivity of this tumour entity to oxaliplatin [3]. At equimolar concentrations, the drug forms fewer DNA adducts than cisplatin, but these adducts appear to be more efficient in the inhibition of DNA synthesis [4]. As already mentioned above, oxaliplatin cross-links adjacent guanine and adenine base pairs similarly to cisplatin but due to its bulkier carrier ligand it induces a different distortion on the DNA helix. Cellular machinery processes oxaliplatin-DNA adducts differently than cisplatin-DNA adducts. For instance, the former are not recognised by the mismatch repair proteins, so that oxaliplatin activity is MMR-independent [3]. A recent study has discovered another striking feature of oxaliplatin: the drug appears to exert its effect through induction of ribosome biogenesis stress, and not via DNA damage response. The authors claimed that dependence of colorectal cancer cells on translational machinery (they called it „translational addiction") accounts for oxaliplatin efficacy in this tumour type [74].

Mathé et al. evaluated oxaliplatin on a panel of murine tumours. Oxaliplatin significantly increased life span in animals with L1210 leukaemia and LGC lymphoma where cisplatin showed little or no activity [75]. They also noted a very low incidence of nephrotoxic side effects. Later, the same team initiated a Phase I trial to determine the maximally efficient dose range between 45 and 67 mg/m^2. In this first trial, gastrointestinal toxicity in the form of nausea and vomiting was observed and seemed a dose-limiting toxicity at that time [76]. Yet, in this study oxaliplatin was evaluated as a single agent.

Levi and colleagues combined oxaliplatin with 5-fluorouracil and leucovorin (folinate) in a Phase II trial in 93 patients with metastatic colorectal cancer. All patients previously received either chemo- or radiotherapy. In 58 % cases, objective response was observed. The dose-limiting toxicities were diarrhoea (19 %) and vomiting (35 %). Already in this study pronounced peripheral sensory neuropathy was noticed as 14 out of 93 patients had to discontinue treatment [77]. In a following Phase II trial in patients with advanced colorectal cancer resistant to the 5-FU / folinate combination, oxaliplatin-based regimen was further developed to establish FOLFOX2. The schedule included a 2 h infusion of 100 mg/m^2 oxaliplatin together with 500 mg/m^2 leucovorin followed by a 48 h infusion of 1500 mg/m^2 5-fluorouracil (increased to 2000 mg/m^2 if no pronounced toxicity was observed) every two weeks. The overall response was rather high (46 %), neutropenia (39 %) and peripheral sensory neuropathy (9 %) were dose-limiting [78]. This study

likely served as a basis for approval of the drug in France. A later trial conducted between October 1995 and December 1996 compared two improved dose schedules, FOLFOX3 and FOLFOX4. The FOLFOX3 consisted from an infusion of 85 mg/m^2 oxaliplatin combined with 500 mg/m^2 leucovorin for 2 h followed by a 22 h infusion of 1500 mg/m^2 5-fluorouracil. On the following day, only folinate and 5-FU were repeated. The FOLFOX4 had a similar structure but the dose of leucovorin was reduced to 200 mg/m^2, the dose of continuous infusion of 5-FU was decreased to 600 mg/m^2 but supplemented with 400 mg/m^2 5-FU bolus (Figure 8). A higher response rate was observed on FOLFOX4 than on FOLFOX3 (23.5 % vs. 18.4 %, respectively). The median overall survival was also longer (11.1 vs. 10.6 months). Although the incidence of Grade 3 peripheral neuropathy was also significantly higher on FOLFOX4 (36.9 % vs. 15 %, p=0.02), the latter was seen as a more advantageous regimen [79]. And it is the one still commonly used nowadays.

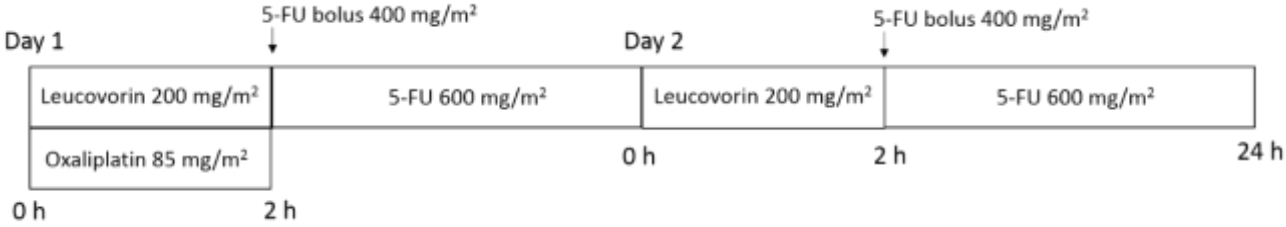

Figure 8. Schematic representation of the FOLFOX4 dose regimen.

Oxaliplatin under the trade name Eloxatin® was first approved for the second-line treatment of metastatic colorectal cancer in a national procedure in France on April 12, 1996. The marketing authorisation holder was Sanofi Aventis [80]. The authorisation for the first-line therapy followed in April 1998. In 1999, Eloxatin® received approval for advanced colorectal cancer in major European states through a Mutual Recognition Procedure. France served thereby as a reference member state [81]. In Germany, the application was submitted on March 9 and approved on August 25 [47] . The FOLFOX4 therapeutic regimen was adopted in December 2003, again in a Mutual Recognition Procedure. An extension of therapeutic indication to include adjuvant treatment of stage III (Dukes' C) colon cancer after complete resection of primary tumour followed in September 2004 [81]. This broadened indication is also the one specified in the AMIS database as of December 1, 2008 [47].

This time platinum drug approval in the USA came later than in Europe. For oxaliplatin, full review reports are available. The IND (Investigational New Drug) submission was filed at the FDA by Axiom, Inc. in February 1993. After its short-lasting transfer to Debiopharm SA, it was finally acquired by Sanofi-Synthelabo in April 1995. Shortly thereafter the IND was placed on clinical hold due to CMC (Chemistry, Manufacturing, and Control) issues. The hold was lifted only in May 1997 [82].

When the New Drug Application (NDA) 21063 was submitted in February 1999, the clinical assessment raised major concerns. The results of two randomised clinical studies were presented in support of the application, EFC 2961 with n = 100 / arm and EFC 2962 with n = 210 / arm. Both of them compared a 5-fluorouracil / leucovorin arm with the combination therapy consisting of oxaliplatin, 5-fluorouracil and folinic acid. However, different regimens were adopted in the two trials. While a chronomodulated infusion with or without oxaliplatin for five consecutive days was

used in EFC 2961, oxaliplatin / leucovorin infusion was followed by 5-fluorouracil in the other study [82].

None of these trials considered overall survival as a primary endpoint. EFC 2961 was designed to demonstrate improved tumour response, and EFC 2962 focused on disease-free survival. Response rates were significantly higher in oxaliplatin-containing arm than on the comparator in EFC 2961 ($p<0.001$) and were 39 % and 13 %, respectively, as determined by investigator (the FDA values were 37 % and 14 %, respectively). In EFC 2962, modest but statistically significant increase in progression-free survival was observed (6.2 vs. 8.8 months, $p = 0.0001$, investigator assessment, expert assessment was similar). However, in both studies analysis of overall survival data showed no advantage of the oxaliplatin arm. The limited power of the studies most likely accounted for the absence of positive results in terms of overall survival [83]. Moreover, the data was presented at the Oncologic Drugs Advisory Committee (ODAC) meeting at the FDA in March 2000. At the same meeting, the data demonstrating survival advantage for irinotecan as first-line treatment of metastatic colorectal cancer were shown. Since the indication was the same, irinotecan was favoured, and approval for oxaliplatin was not recommended. In May 2000, Sanofi-Synthelabo withdrew the NDA [82].

Later in 2000, the company sought a scientific advice from the agency in an End-of-Phase-2 meeting. The focus was on the clinical development program. The FDA insisted on evaluating oxaliplatin in combination with 5-FU and leucovorin in comparison to the fluoropyrimidine regimen and with the platinum drug alone. Survival benefit was seen as a required primary endpoint, nevertheless, the FDA agreed to consider accelerated approval based on response rate. As irinotecan was already approved by then, the study needed to enrol exclusively the patients who progressed on the irinotecan-based treatment. According to the initial view of the FDA, recurrent patients had to be excluded. Thus, clinical trial EFC 4584 was designed in accordance with the suggestions of the agency. Two phases of the study were envisaged. In the first phase, response rate was to be evaluated, in the second overall survival was to be assessed. In July 2001, an amendment to the study protocol allowed to enrol all patients with prior irinotecan-based therapy, either progressing or relapsed [82].

The preliminary data from EFC4584 trial showed that response rates were better on oxaliplatin-based combination than with any other treatment available for metastatic colorectal cancer patients progressing on first-line irinotecan with 5-fluorouracil / leucovorin. For this reason, the FDA granted oxaliplatin a fast track designation on April 11, 2002 [82].

The new NDA 21492 was submitted by Sanofi-Synthelabo on June 24, 2002. It was handled as a priority application since there was no efficient treatment of patients with metastatic colorectal carcinoma after prior therapy with irinotecan. Moreover, there was evidence of better response rates on oxaliplatin as mentioned above [82].

Upon assessment, there were no CMC issues as the compound was already known from the marketing authorisation and approved use in Europe and other countries (in total 60 countries by December 31, 2001). Stability issues were discussed: while lyophilised powder is stable for 36 months, reconstituted drug can be stored only for 24 h at 2 to 8 °C and has to be used within 6 h after final dilution of the reconstituted medicine if the dilution is kept at room temperature. However, since this was (and is) explicitly mentioned in the summary of product characteristics,

no concerns were raised. As pharmacological / toxicological assessment was concerned, there were also no open issues. Broad spectrum of in vitro cytotoxicity and in vivo antitumour activity in a variety of models including those resistant to cisplatin had been shown. Already in pre-clinical studies synergistic interaction with 5-fluorouracil was evident. This synergism was likely due to the reduction of 5-FU catabolism by oxaliplatin, which in turn was the consequence of the decreased level of thymidylate synthase. The mechanism is reflected in the therapeutic regimen for oxaliplatin / 5-FU combination as the platinum drug is administered before the fluoropyrimidine. The Ames test in bacteria was negative but other genotoxic tests were positive for oxaliplatin. The drug was found mutagenic in mammalian cells in vitro (L5178Y mouse lymphoma assay) as well as clastogenic in vitro according to the chromosome aberration test and in vivo in mouse micronucleus assay. Carcinogenicity was the drug was not evaluated because of its obvious genotoxicity and its indication for treatment of advanced cancer. Oxaliplatin caused developmental mortality and adversely affected foetal growth in rats. The summary of product characteristics pointed out potential hazard for the foetus and advised women with childbearing potential to avoid becoming pregnant during treatment with oxaliplatin. As no information was available on possible excretion of the substance in human milk, product information suggested either to interrupt nursing or to delay drug administration [82].

The major clinical study to support licensing of oxaliplatin in the USA was the above-mentioned EFC4584. It was a large (to avoid the problem of being underpowered), multicentre, randomised Phase III trial with three arms: 5-FU / leucovorin, oxaliplatin alone, and oxaliplatin / 5-FU / leucovorin combination as second-line treatment of metastatic colorectal carcinoma. The study was carried out in two parts. In the first phase, response rate was analysed in all patients recruited by then, with at least 150 patients in each arm. The second part planned to evaluate overall survival in the full sample size (n= 786). The dosing schedule in the combination arm followed the FOLFOX4 regimen shown in Figure 8. The treatment was planned as two-week cycles with total duration up to one year. Tumour regression was evaluated based on a computer tomography or a magnetic resonance imaging scan. The NCI RECIST (National Cancer Institute Response Evaluation Criteria in Solid Tumours) criteria were applied to assess response. The efficacy analysis was performed with all patients who received study drugs, whereas safety was evaluated in all patients who received at least one dose of study drugs. Primarily, the trial aimed at comparison the 5-FU arm with the combination arm. In addition, single-agent oxaliplatin was compared with the 5-FU arm. The comparison of oxaliplatin alone with the combination was planned in the case oxaliplatin combination showed advantage over 5-FU. Although overall survival was the primary endpoint of the trial, the data were not mature at the time of the NDA. However, the FDA had previously agreed to accept response rates as a basis of an accelerated approval. Small but statistically significant ($p=0.0002$) improvement was seen in the combination arm. The response rates were 0 % in the 5-FU arm (confidence interval CI 0 – 2.4 %, n=151), 1 % on single agent oxaliplatin (CI 0.2 – 4.6 %, n=156), and 9 % upon combination (CI 4.6 – 14.2%, n=152). Thus, the inclusion of single-agent oxaliplatin arm allowed to clearly demonstrate synergism between the platinum drug and 5-FU. The time-to-tumour-progression analysis also showed a significant advantage ($p<0.0001$) of the combination (median 4.6 months, CI 4.2 – 6.1, n=152) over the fluoropyrimidine-based therapy (median 2.7 months, CI 1.8 – 3.0, n=151). In its concluding remarks regarding efficacy, the FDA mentioned that the results of the trials from the previous NDA 21063 were supportive of the results of EFC4584 study [82].

Safety findings suggested that neurotoxicity was dose-limiting although it was reversible and mostly did not interfere with daily activities. The incidence was high both on single-agent oxaliplatin (76 %) and upon combination (74 %), while little toxicity was observed in the 5-FU arm (17 %). Most neurotoxicity in the combination was acute (78 % of total neurotoxicity events) with many patients having a persistent event (48 % of all patients, 65 % of total neurotoxicity events). Whereas the incidence of acute neurotoxicity remained stable during the treatment, the proportion of persistent neurotoxicity increased with cycle number. The majority of patients continued therapy without dose reduction despite the adverse events. Nevertheless, dose reduction suggestions were included in the summary of product characteristics [82].

The major haematological toxicity was neutropenia. The proportion of patients experiencing Grade 3 and 4 neutropenia was much higher in the combination arm (44 %) than either with single-agent oxaliplatin (0 %) or 5-FU / leucovorin (4.9 %). As in the case of the other two platinum drugs, nausea and vomiting were common but could well be controlled with 5-HT_3 receptor antagonists and / or dexamethasone. The addition of oxaliplatin to 5-fluorouracil appeared to increase the incidence of the 5-FU-related diarrhoea (11 % Grade 3/4 diarrhoea in the combination arm vs. 4 % with oxaliplatin alone and 3 % on 5-FU / leucovorin) [82].

Similarly to cisplatin and carboplatin, oxaliplatin is mostly renally excreted. As could be expected, renal impairment led to a larger increase in total platinum exposure in plasma resulting in possible deleterious effects on safety. For this reason, a cautionary statement regarding administration in patients with renal failure was included in the product information [82].

Taken together, the FDA found that oxaliplatin in combination with 5-FU and leucovorin showed efficacy and a tolerable adverse effect profile in metastatic colorectal cancer patients who had progressed on or relapsed after the irinotecan / 5-FU / leucovorin regimen [82].

However, the approval was not without obligations. The company took several Phase 4 commitments. These included the completion of the EFC4584 study and submission of mature overall survival data, completion of other ongoing studies, examination of the safety of the final dosage of 85 mg/m^2, and setting up an educational program to reduce potential medication errors resulting from mistaken use of oxaliplatin instead of carboplatin [82].

Interestingly, instead of submitting the final data of the trial EFC4584 the company submitted the results of another study EFC7462 conducted in patients with metastatic carcinoma of colon or rectum after prior therapy with irinotecan. It provided an opportunity to broaden the therapeutic indication. Although the FDA preferred overall survival, the primary endpoint was time-to-tumour-progression with survival and response rate being secondary endpoints. Nevertheless, FOLFOX4 showed significantly ($p<0.0001$) longer survival (19.4 months) than purely fluoropyrimidine-based regimen (14.6 months). In 2007 and 2008, variations with new clinical data were submitted but the commitments regarding the above-mentioned safety study and the medication error educational program remained unfulfilled. On January 31, 2005, a new formulation was approved but no further clinical studies were submitted [82].

Locally approved drugs

An overview of the platinum drugs approved in single countries is given in Table 3 and their chemical structures are shown in Figure 9. The drugs and their approval history are discussed in detail below.

Table 3. Locally approved platinum-based drugs (modified from [1]).

Drug	Other names / brand names	Originator company	Dose-limiting toxicity
Nedaplatin	254-S Aquapla®	Shionogi Pharmaceuticals	Myelosuppression
Lobaplatin		ASTA Medica	Thrombocytopenia
Heptaplatin	SKI 2053R Sunpla® Eptaplatin	SK Chemicals	Nephrotoxicity

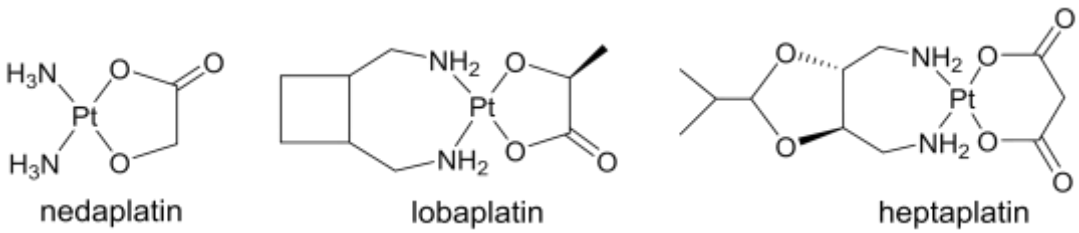

Figure 9. Chemical structures of the locally approved platinum-based drugs.

Nedaplatin

Nedaplatin was first prepared by Totani et al. in Japan [84]. The drug was further developed by the Japanese company Shionogi Pharmaceuticals [85]. A human tumour clonogenic assay showed promising cytotoxicity in four cell lines derived from non-small cell lung carcinoma patients [86]. Comparison of nedaplatin with cisplatin in vivo in murine ascites L1210 leukaemia and a solid Lewis lung carcinoma model showed comparable growth inhibition effect of the two compounds, with nedaplatin causing less toxic side effects [87]. In a Phase II trials, the response rates of 42.2 % (head-and-neck cancer), 40.9 % (small cell lung cancer), 20.5 % (non-small cell lung cancer), 38.1 % (bladder cancer), 80.0 % (testicular cancer), 37.3 % (ovarian cancer), 46.3 % (cervical cancer), and 51.7 % (oesophageal cancer) were observed. The incidence of toxicity was relatively low: 28.5 % for thrombocytopenia, 21.1 % for leucopenia, 16.8 % for anaemia, and 18.5 % for nausea and vomiting. Based on these data, the Japanese authority PMDA (Pharmaceuticals and Medical Devices Agency) approved nedaplatin for use in the above-mentioned indications in 1995 [1,88]. The PMDA does list information on the approved drugs but the data goes back only up to 2004 [89]. The reason for not going for a worldwide approval was probably the experience with carboplatin. As is clear from the above, mature overall survival data were required for the FDA approval, and solely more favourable toxicity profile did not suffice.

Lobaplatin

Lobaplatin was designed by ASTA Medica (Degussa) in Germany [90], and the first report on this compound dates back to 1990 [91]. It possesses a diamine chelate carrier ligand, which, in contrast to oxaliplatin, represents a mixture of diastereomers with S,S- and R,R-configuration [1]. It showed cytotoxicity in a low micromolar range in a broad range of cancer cell lines. In vivo, the compound had a great anticancer activity against the cisplatin-resistant P388 tumour in mice. The measurements of blood urea indicated no nephrotoxic side effects [91]. Stability studies of lobaplatin in infusion media showed that the drug is more stable in saline (12 h at room temperature and 24 h at 4 °C) than in 5 % dextrose ($p<0.005$) [92]. A larger preclinical screen suggested that lobaplatin overcomes cisplatin resistance in testicular and ovarian cancer in cancer cell lines and animal models [93]. In a Phase I trial, responses were seen only in two out of 27 patients with refractory solid tumours. Thrombocytopenia was dose-limiting, whereas no renal impairment was detected [94]. Nevertheless, these findings stimulated Phase II trials in ovarian cancer. One Phase II study in refractory ovarian cancer reported the overall response rate of just 7 % [95], however, in another trial the response was with 24 % more pronounced [96]. Both studies reported thrombocytopenia as a major and dose-limiting toxicity. There were also trials with negative outcome: in a study conducted by the MD Anderson Cancer Center, no objective responses were detected [97].

As ASTA Medica discontinued development, it was taken over by Zentaris AG formed in 2001 from the biopharmaceutical, gene therapy and inhalation technology units of ASTA Medica. Zentaris was in turn acquired by AEterna Laboratories in December 2002. In January 2003, Zentaris signed a US $4.3 million contract with Hainan Tianwang International Pharmaceuticals for manufacturing and marketing the drug in China. Lobaplatin was approved in this country for treatment of chronic myelogenous leukaemia (CML) and inoperable, metastatic breast and small cell lung cancer [98]. However, it is completely unclear, which data served as a basis for the approval. The Medline® literature database does not list any clinical trials with lobaplatin in CML. A Phase II trial in 19 patients with metastatic breast cancer in 2013 showed partial response only in two patients [99]. However, a recent study demonstrated a significant advantage from adding lobaplatin to the docetaxel / epirubicin ($p=0.001$) in triple-negative breast cancer in a neoadjuvant setting: pathological complete response rate increased from 12.7 % to 38.7 %. No survival data were presented but the incidence of recurrence and metastases was significantly lower in the lobaplatin arm ($p=0.028$) [100]. The available data for small cell lung cancer is not convincing. An analysis of results from one centre of a multi-centred one-arm Phase IV study in China based on thirty first-line patients reported an overall response rate of 57 % [101]. However, full study data has not yet been reported. Taken together, limited evidence of efficacy has likely prevented the worldwide approval of lobaplatin.

Heptaplatin

Heptaplatin was first mentioned in the literature as compound SKI 2053R when the results of the first preclinical studies were reported. In human lung cancer (PC-9 and PC-14) and stomach cancer (MKN-45 and KATOIII) cells, the compound exhibited cytotoxicity similar to that of cisplatin [102]. Heptaplatin was able to largely circumvent resistance in the L1210 cisplatin-resistant leukaemia

xenograft in mice. In the KATOIII stomach adenocarcinoma murine model, the tumour growth inhibition rate was comparable to that of cisplatin (65 % and 59 %, respectively) [103]. Safety pharmacology studies showed no effect of the new drug on nervous, cardiovascular, respiratory and gastrointestinal system [104]. Heptaplatin was shown to be embryotoxic at minimal maternally toxic dose in Sprague Dawley rats [105]. However, it appeared not to cross the blood-placenta barrier [106]. In a Phase II trial in gastric cancer published in 1999, response rate of 17 % (six out of 35 patients) was observed, and no Grade 3 or 4 toxicities were detected [107]. It is not known whether these data served as a basis for approval by the Korean Ministry of Food and Drug Safety but SK Chemicals received a marketing authorisation for the drug product for the treatment of gastric (stomach) cancer on July 14, 1999 [108]. A parallel Phase II trial in non-small cell lung cancer showed a comparable response rate (16.2 %) in a patient population of a similar size (37 patients) and also no severe toxicity [109]. It remains unclear why this indication was not included.

New drug candidates

The structures of new drug candidates, which have been evaluated in clinical trials, are presented in Figure 10. Drug development is discussed in detail in the following sections.

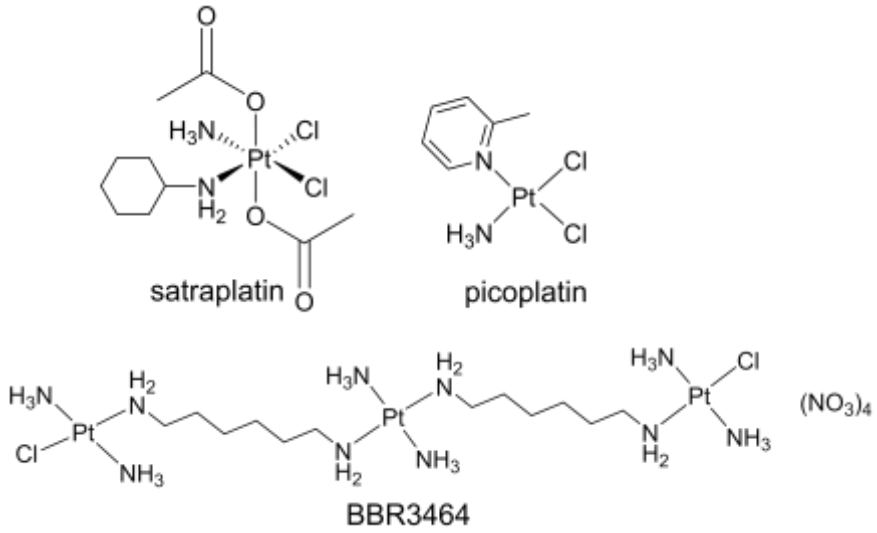

Figure 10. Chemical structures of the platinum-based drug candidates.

Satraplatin

Satraplatin was developed in a collaboration of Bristol-Myers Squibb, Johnson Matthey and Institute of Cancer Research. The primary aim was to develop an orally active platinum drug, not cross-resistant with cisplatin and having a safety profile similar to that of carboplatin. Satraplatin (compound JM216) was rationally designed based on the desired properties. The lipophilic axial ligands ensure oral absorption, and asymmetric carrier ligands account for a different structure of DNA adducts as compared to cisplatin. One could note that satraplatin also possesses chlorides as leaving groups, similarly to cisplatin. However, in blood satraplatin first loses its axial ligands in a process of reduction by proteins and forms its major metabolite JM118. A prior ligand exchange is also very extensive resulting in a number of other metabolites (Figure 11). Although the metabolism of satraplatin is fast (no drug can be detected in plasma already three hours after administration), the actual formation of the active species is slower than in the case of cisplatin [110].

The diaqua species of satraplatin bind to DNA inhibiting its replication and transcription. DNA damage triggers a cell cycle arrest in the G2 phase and induction of apoptosis. Satraplatin-DNA adducts are detected by the nuclear excision repair, but not by the mismatch repair proteins. Some studies reported that satraplatin-DNA crosslinks are not recognised by HMG proteins, in contrast to cisplatin. This may explain a different spectrum of activity of satraplatin [111]. The detoxification of the drug occurs mainly through its conjugation to glutathione. Consequently, elevated GSH levels confer resistance to satraplatin [110].

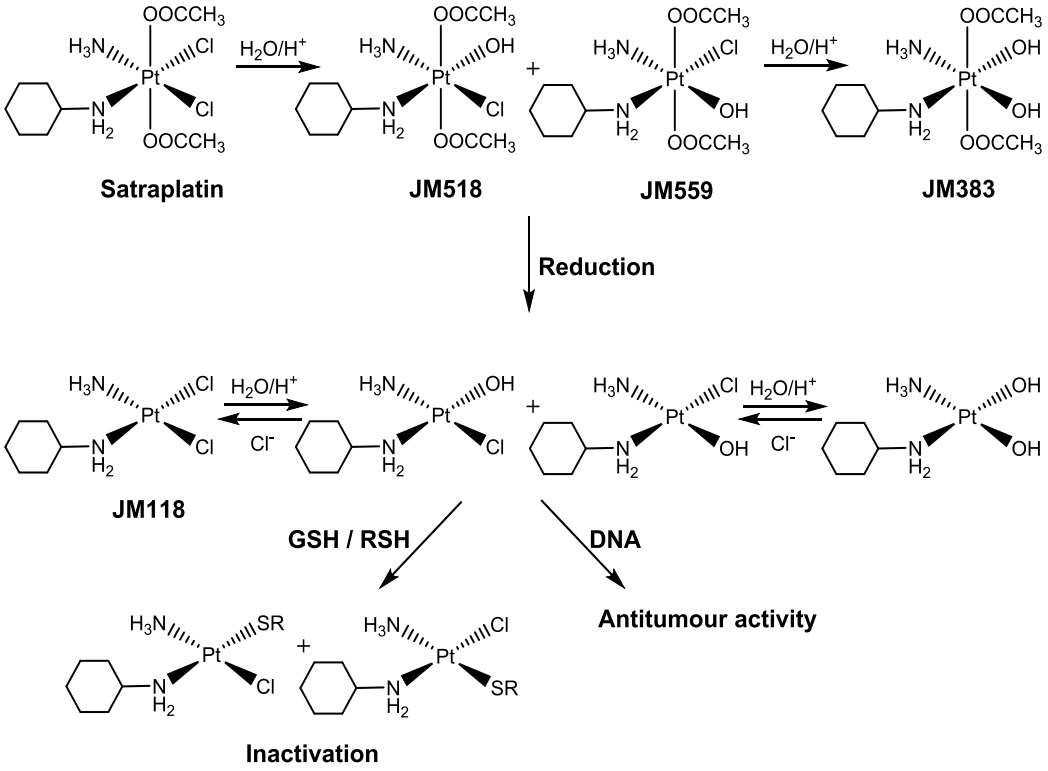

Figure 11. Metabolism of satraplatin (modified from [110]).

In vitro screening on a panel of tumour cell lines (including leukaemia, small and non-small cell lung cancer, melanoma, colon, renal and ovarian carcinoma) showed remarkable activity in most entities, sometimes surpassing the potency of cisplatin almost by tenfold [110,111]. It retained activity in cisplatin-resistant cell lines, also in those with defects in cisplatin accumulation, implying that satraplatin employs a different mechanism of cellular entry [110]. Satraplatin possessed activity against hormone-refractory prostate cancer, and its metabolite JM118 was even more potent. In several cell lines, satraplatin overcame cisplatin and taxane resistance [111]. In vivo, the drug showed activity in a number of tumour models. Intravenous administration was compared with the oral route in ADJ/PC6 plastocytoma model, also used in the development of carboplatin. No loss of activity due to oral administration was observed. Interestingly, satraplatin remained active against cisplatin-resistant variant of this tumour, although with reduced potency [110]. An important preclinical study guided the dosing schedule in clinical trials. Mice bearing ovarian carcinoma xenograft were given satraplatin either as a single dose or splitted in five doses or as a chronic daily dose. The growth delay was the most pronounced with the splitted dose (30 vs. 91 vs. 16 days, respectively) [110]. Independently of the schedule, the dose-limiting toxicity was myelosuppression. Interestingly, on the single dose leucopenia was the most pronounced, and on the splitted dose thrombocytopenia predominated. No signs of nephrotoxicity as with cisplatin or neurotoxicity as with oxaliplatin were detected on either schedule [110].

A first Phase I study started in London in 1992 but it was soon discontinued: due to non-linear pharmacokinetics the maximum tolerated dose was reached. However, partial response was detected in some relapsed ovarian cancer patients. The most pronounced adverse effects were attributed to myelosuppression. In the view of this study, the following trials adopted a splitted dose schedule as was done in preclinical investigations in mice. But in such studies with single agent satraplatin, surprisingly no responses were detected [110]. On the contrary, in another

Phase I trial in squamous cell carcinoma of the head and neck, complete response was seen in seven out of eight patients receiving satraplatin in combination with radiotherapy [1]. Yet a Phase II trial in small cell lung cancer showed 38 % partial response with a single agent satraplatin administered 120-140 mg/m^2/day on five consecutive days [1,110]. With 64.7 % incidence rate, leucopenia was the most common [110]. With a similar dosing regimen, 31 % partial response was achieved in hormone-refractory prostate cancer. A Phase II study in patients with recurrent ovarian cancer, satraplatin was compared with cisplatin or carboplatin (depending on prior therapy). In both arms, the objective response rates of 35 % were found indicating similar efficacy [111]. A large Phase III study in hormone-refractory prostate cancer was designed for 380 patients but was terminated by Bristol-Myers for business reasons. Only 50 patients could be evaluated. Compared to placebo/prednisone, an increase in progression-free survival (5.2 vs. 2.5 months, $p=0.023$) and overall survival (14.9 vs. 11.9 months, $p>0.05$) was reported in the satraplatin/prednisone arm [112]. These rather preliminary results likely determined the choice of indication, when the drug was taken over by Spectrum Pharmaceuticals in January 2002. Johnson Matthey licensed satraplatin to this company after Bristol-Myers Squibb discontinued development. The drug was further sublicensed to GPC Biotech in October 2002 [113].

The company completed a Special Protocol Assessment with the FDA, and satraplatin received the fast track status for the 2nd line treatment of hormone-refractory prostate cancer (HRPC) after failure of taxane-based treatment because there was an unmet clinical need (no standard therapy was approved by then for this indication). At that time, Phase II trials in HRPC, ovarian and small cell lung cancer were finished. The decisive Phase III SPARC (Satraplatin and Prednisolone Against Refractory Cancer) trial enrolled target population and was ready to get underway. The fast-track status allowed the FDA to accept a rolling NDA. A rolling NDA according to Section 506 (c) of the 1997 Act implies submission of parts of an NDA (e.g. CMC, non-clinical, clinical) separately. On December 15, 2005, GPC Biotech started a rolling NDA. On July 12, 2006, the non-clinical section was submitted. Finally, the clinical part completed the NDA on February 16, 2007. The FDA accepted the submission for filing and granted satraplatin priority review (accelerated approval procedure) on April 16. Although some improvement in progression-free survival was seen in the SPARC trial, the Oncologic Drugs Advisory Committee advised the FDA to wait for the overall survival analysis on July 24. GPC Biotech appeared confident at first, however, it withdrew the NDA already on July 30 [114].

The respective assessment report is unfortunately not available, as the FDA lists only approved drugs. On the contrary, the European public assessment report of the European Medicines Agency (EMA) is freely accessible. Similarly to the United States, the marketing authorisation application in the European Union eventually resulted in the withdrawal of the application by the company.

Pharmion Ltd. received rights to satraplatin in the European Union in December 2005. Prior to the marketing authorisation submission, scientific advice was obtained from the EMA and several national competent authorities. There were no objections on the CMC part. As the drug substance was new, the information was provided in the Active Substance Master File. As the drug product was concerned, microcrystalline satraplatin did not show better efficacy than the product formulated without particle size reduction. Nevertheless, the company was requested to ensure consistency of manufacturing and product performance [113].

The non-clinical section was also found approvable. As mentioned above, satraplatin showed promising antitumour activity in several cancer cell lines including some cisplatin-resistant models. In vivo evaluation in PC-3 xenografts and several other models was positive. Potentiation of antitumour activity and synergism were found in combination with paclitaxel, docetaxel and radiation. In safety pharmacology studies, no acute side effects were observed [113].

The conversion of satraplatin to its main metabolite JM118 was reported to be catalysed by haem proteins in red blood cells, CYP (cytochrome P450) oxidoreductase and several CYP enzymes including CYP3A4. Although IC_{50} of CYP3A4 inhibition exceeded plasma concentrations of satraplatin, CYP3A4 suppression in the gut in the event of high local exposure was considered feasible and requiring clarification [113].

Toxicological studies aimed at the determination of the maximum tolerated dose instead of a no observed effect level. In both rodent and non-rodent species, primarily effects on lymphoid organs and gastrointestinal lesions were observed. The haematological parameters were also affected, e.g. leucocyte and platelet count were decreased. However, this reduction was reversible upon therapy cessation. Some emesis was detected in dogs but could be well controlled with ondansetron. The animals tested experienced adverse irreversible effects on spermatogenic cells and testes [113].

Satraplatin was found unequivocally genotoxic in the standard three-test battery (consisting of a bacterial reverse mutation test, a cytogenic test for chromosomal damage, and an in vivo test for genetic damage). No carcinogenicity study was submitted, which was considered acceptable, nevertheless, evidence of carcinogenic potential of satraplatin was rather convincing since increased number of malignancies were detected in the course of the treatment. At maternally toxic doses the drug induced embryotoxicity in rats and rabbits and skeletal developmental variations in rat foetuses [113].

The clinical part of the dossier presented safety and efficacy data to support the application. Both effects were assumed to be controlled by free platinum species. Protein binding was found be irreversible and faster with JM118 than with satraplatin itself. As mentioned above, the metabolic pathways were not sufficiently clarified, which was however not considered a major issue in the assessment. In any event, metabolites appeared to be mostly renally excreted. That led to enhanced platinum exposure in patients with renal impairment. Therefore, the Agency asked to specify dose reduction for such patients. Furthermore, the applicant was requested to elucidate possible CYP3A4 inhibition in the gut and the effect thereof on drug-drug and food-drug interactions [113].

The data from the pivotal, randomized (2:1), double-blind, placebo-controlled Phase III SPARC trial mentioned above formed the basis of the marketing authorisation application. Some other studies were conducted but were considered of little value because of the early termination by the original sponsor Bristol-Myers Squibb. The SPARC trial compared satraplatin in combination with prednisone vs. placebo / prednisone as 2nd line treatment of HRPC. When SPARC study was enrolling and even when the study started, docetaxel was not yet approved for the 1st line treatment of HRPC. But the approval of docetaxel for HRPC in the meantime changed the situation completely. As a result of the altered state-of-art for HRPC, the claimed indication for satraplatin was adjusted to encompass only 2nd line therapy after failure of docetaxel. However,

only 51.4% of all patients in the SPARC trial were pre-treated with docetaxel, so that only the half of the study population was in principle eligible to be analysed for the claimed indication. The two co-primary endpoints of the study were overall survival and progression-free survival [113].

The original submission of the marketing authorisation application included the analysis of progression-free survival (PFS) of 802 of total 950 patients (valid events) and the interim overall survival data (as of June 15, 2006). In the response to the CHMP (Committee for Medicinal Products for Human Use) day 120 list of questions, the final results on overall survival (cut-off September 21, 2007) were presented. Thereby the total patient population, both docetaxel-treated and -untreated, was considered. For the PFS analysis, disease progression was defined as a composite endpoint and implied the first occurrence of one of the following:

- tumour progression, radiographically assessed,
- skeletal event-related progression,
- symptomatic progression such as pain increase or weight reduction,
- death.

This composite definition of disease progression is more prone to an investigator bias, especially the determination of symptomatic progression. It becomes especially important if one considers that adverse events anticipated in the satraplatin arm could have compromised the double-blind nature of the study.
Of the 802 evaluated patients, 528 belonged to the platinum arm and 274 to the placebo arm. There was a comparable proportion of radiographic progression in both groups (35.8 % vs. 36.9 % in satraplatin and placebo, respectively) but less pain progression on satraplatin (34.3 % vs. 42.7 %). The evaluation of progression-free survival showed significant advantage of satraplatin ($p<0.001$) with the mean PFS of 24.9 weeks on the platinum drug and 16.2 weeks on placebo. Also a significant reduction of the risk of progression by 33 % was observed (hazard ratio HR=0.67, confidence interval CI 0.57 – 0.77, $p<0.001$). This decrease, however, does not automatically transfer into the clinical benefit as the difference between the two Kaplan-Meier curves became apparent only after 10 weeks of the therapy and at that time the half of the patients already progressed. Moreover, the median PFS was not significantly different showing only a negligible advantage of 9.8 days in favour of the satraplatin arm (11.1 vs. 9.7 weeks, respectively) [113].
The final overall survival data did not reveal any significant differences between the two study arms (61.3 weeks on satraplatin vs. 61.4 weeks on placebo, p=0.799, HR=0.97). In response to the CHMP day 120 list of questions, the applicant submitted the subgroup analysis to distinguish between docetaxel-treated and -untreated patients. Even though the patient population was not stratified according to docetaxel pre-treatment, the two groups were well balanced: 51.5% in the satraplatin arm received prior treatment vs. 51.1% in the placebo arm. There were no significant differences in overall survival irrespective of the pre-treatment status. The median survival after prior docetaxel was 66.1 and 62.9 weeks on satraplatin and placebo, respectively (p=0.399), and without previous docetaxel therapy 58.0 and 58.6 weeks, respectively (p=0.784). As PFS results were concerned, the subgroup analysis was in line with the overall population. The significant decrease in the risk of disease progression was found. However, the median PFS was not different in either pre-treatment group: 10.1. vs. 9.1 weeks for satraplatin and placebo, respectively, after prior docetaxel, and 12.3 vs. 10.1 weeks, respectively, in patients who received no docetaxel before [113].

Regarding safety, the incidence of study-drug related adverse events was higher in the satraplatin group as compared to placebo (78.9 % vs. 36.7 %, respectively) as could be expected from the experience with other platinum drugs. The proportion of serious adverse events was thereby also higher in the platinum arm (8.7 % vs. 3.2 %). The observed side effects were those already seen in pre-clinical models and known from other platinum-based drugs. These included haematological (thrombocytopenia 32 %, neutropenia 28.3 %, and anaemia 24 %) and gastrointestinal (nausea 28.8 %, diarrhoea 23.8 %, constipation 22.7 %, and vomiting 16.4 %) adverse effects. Fatigue was also common (17.5 %) in the satraplatin arm. The incidence of renal failure was rather low; neuro- and ototoxicity were rare and not severe. Overall, increased incidence and severity of adverse events were associated with higher satraplatin dose. The dose-limiting toxicities were anaemia and thrombocytopenia. In general, myelosuppression was the major reason for new or prolonged hospitalisation of patients in the satraplatin group (5.2 % vs. 1.3 % in placebo). The subgroup analysis revealed that the overall frequency of adverse events was comparable in patients who received docetaxel before (89.9 %) and those who did not (92.9 %). Among docetaxel-treated patients compared with untreated ones, the percentage of those experiencing fatigue (23.6 % vs. 11.1 %, respectively), gastrointestinal side effects (62.7 % vs. 52.8 %, respectively), and hepatic toxicity (8.4 % vs. 3.3 %, respectively) was higher. This was considered especially relevant since satraplatin would be indicated in patients after prior docetaxel therapy and all patients receiving the platinum drug would suffer from an increase in incidence and severity of adverse events [113].

In conclusion, the Agency highlighted the absence of advantage of satraplatin in terms of overall survival as an objective parameter for clinical benefit. It also noted that a composite PFS endpoint is a subject to the investigator bias and cannot therefore be seen as a valid endpoint. Safety profile was found consistent with that of other platinum drugs, most similar to carboplatin. The assessment reads that "as outlined by the EMEA guidelines, 'licensing based on one pivotal study, requires demonstration of efficacy at levels beyond standard criteria for statistical significance' (CPMP/EWP.205/95/Rev.3; CHMP/EWP/2330/99)" [113]. This was not the case with satraplatin. When no survival benefit can be expected, then quality of life and reduction in disease symptoms gain importance. However, in the target population for the claimed indication increased incidence of adverse events was already expected due to pre-treatment with docetaxel. There were further no data to support positive impact of satraplatin on quality of life. For these reasons, the overall benefit-risk ratio was found negative, which subsequently led to the withdrawal of the application by the company [113].

Picoplatin

The collaboration between academia and industry, between the Institute of Cancer Research and Johnson Matthey, continued. Extensive research on ovarian carcinoma cell line pairs with acquired cisplatin resistance indicated that scavenging by thiol-containing molecules is one of the major contributors to resistance [112]. Scientists could thus employ a rational design approach aiming at a compound, which would be less prone to deactivation by glutathione and proteins in the cytoplasm. For this purpose, they introduced a bulky carrier ligand. This indeed reduced binding to intracellular thiols as compared to cisplatin [115]. The compound overcame cisplatin resistance in ovarian and lung cancer cells [115,116] and oxaliplatin resistance in colon carcinoma

in vitro [117]. It appeared to circumvent nearly all cisplatin resistance mechanisms known at that time, from reduced cellular accumulation to the loss of mismatch repair and p53 mutations [112]. In human ovarian cancer cell lines, synergistic interaction with paclitaxel was observed [118], and in small cell lung carcinoma cells - with paclitaxel and gemcitabine [119].

The drug product was initially developed by the Canadian biotechnology company AnorMED (a subsidiary of Johnson Matthey) and the compound received a code AMD-473. Further evaluation in a cisplatin-resistant CH1cisR human ovarian xenograft model showed promising antitumour activity, independently of the administration route: either intraperitoneal or intravenous or oral. The dose-limiting toxicity was myelosuppression, with no signs of nephrotoxicity observed. In agreement with the design hypothesis, the rate of protein binding was reduced by 50 % in comparison to cisplatin [120]. The low reactivity also explains a side effect profile similar to that of carboplatin.

The initial Phase I trial was carried out at the Royal Marsden Hospital in London with 42 patients. The results showed a tolerable safety profile with thrombocytopenia and neutropenia being dose-limiting. Two patients had a partial response and five more a prolonged stable disease [112]. In 1998, AnorMED licensed all its rights for production and marketing to the British company Zeneca, which would undergo a fusion with the Swedish Astra a year later to form AstraZeneca known today [121]. Subsequent trials were thus conducted with the company cone ZD0473. All of them did not yield encouraging results. The overall response rate in patients with platinum-sensitive and -resistant small cell lung cancer in a Phase II trial with a single agent reached only 8.3 % and 15.4 %, respectively [122]. In another study in ovarian cancer, an objective response rate of 8.3 % among 59 platinum-resistant and 32.4 % among 35 platinum-sensitive patients was observed [112]. These disappointing data prompted AstraZeneca to return all rights for ZD0473 back to AnorMED. The latter had no financial resources to further develop the drug alone and was looking for a sponsor. So AnorMED licensed the compound to NeoRx, which filed an IND with the FDA for a clinical trial of intravenous drug, now called picoplatin, in patients with resistant or refractory small cell lung cancer. Later the company changed its name to Poniard Pharmaceuticals. In November 2005, Poniard received an Orphan Drug Status for small cell lung cancer from the FDA [123]. The criteria (serious condition, rare disease with less than five cases per 10,000 inhabitants, the absence of fairly efficient alternative methods) were fulfilled. Half a year later, the company completed enrolment for the above-mentioned Phase II trial NCT00116610. Also other trials were initiated. The FDA granted Poniard a Fast Track Designation for intravenous picoplatin in September 2007 [121]. An Orphan Designation in the European Union (EU/3/07/502) followed in December the same year. A significant benefit from possible improvement of the long-term outcome was expected in a rare condition with estimated less than 1.5 cases per 10,000 people [124]. Inspired by first positive clinical results, Poniard initiated a pivotal Phase III SPEAR (Study of Picoplatin Efficacy After Relapse) trial. For this study, Special Protocol Assessment with the FDA was completed. This multi-centred randomised trial aimed at assessment of overall survival as a primary endpoint in ca. 400 patients randomised 2:1 for picoplatin and best supportive care vs. best supportive care alone [112]. In March 2009, the enrolment for the study was finished. In June 2010, final results of the trial were presented at the American Society of Clinical Oncology (ASCO) 2010 Annual Meeting in Chicago. Surprisingly, the trial failed to demonstrate the survival advantage of the picoplatin arm vs. best supportive care (20.6 weeks vs. 19.1 weeks, respectively, p=0.09). It was attributed to the unbalanced high proportion of patients who received post-study

chemotherapy in the best supportive care arm. When only refractory patients (n=273) were considered, i.e. those who showed no response or relapsed within 45 days after the first-line platinum-based chemotherapy, a significant improvement of progression-free survival of two weeks (p=0.03) was found [125]. Nevertheless, the positive opinion of lung oncologists regarding picoplatin was undermined, and Poniard gradually discontinued all ongoing trials. The company withdrew the Orphan Designation in the European Union in 2014 [124].

BBR3464

As mentioned above, already approved platinum complexes induce kinks on DNA, which are recognised among others by the NER system that subsequently repairs DNA damage. Despite different structure of the DNA adducts formed, NER is as efficient with respect to oxaliplatin-DNA adducts as it is for cisplatin crosslinks. The design of polynuclear platinum complexes aimed at compounds capable of the formation of DNA adducts without severe distortion of the double helix. The most promising drug candidate of this class of compounds was BBR3464, a trinuclear platinum complex, in which platinum atoms are connected by a flexible linker. The high net positive charge of BBR3464 facilitates its interaction with phospholipids on the cell surface leading to faster cellular accumulation in sensitive and resistant cells as compared to cisplatin [1]. Several platinum atoms and a flexible structure allows the complex to form long-range delocalised intra- and interstrand crosslinks spanning up to six base pairs [3]. These adducts induce only minor alterations on the DNA helix and are indeed not recognised by the HMG proteins. The intrastrand crosslinks are efficiently repaired by the NER, however, interstrand crosslinks escape recognition and excision [126,127]. Recognition of the DNA adducts with the trinuclear complex by p53 induces a different cellular response, which explains its activity in cisplatin-resistant cells with p53 mutations [128].

In vitro activity of the new compound was impressive, it showed cytotoxicity in low nanomolar range and overcame cisplatin resistance in glioma, neuroblastoma, melanoma, ovarian and lung cancer [1]. Evaluation of BBR3464 on the NCI panel of cancer cell lines clearly demonstrated a different activity spectrum than that of cisplatin [3]. In mice bearing cisplatin-resistant GFX214 and MKN45 gastric carcinoma xenografts, the compound was highly potent, and tumour growth inhibition persisted also after drug administration was discontinued. However, already in these preclinical studies it was clear that the maximum tolerated dose of BBR3464 was an order of magnitude lower than of cisplatin [129]. This strong systemic toxicity was further confirmed in Phase I trials where dose-limiting levels of neutropenia and gastrointestinal toxicity were quickly reached [130,131]. Therapeutic response in Phase II trials in ovarian, gastric and small cell lung cancer was only sporadic, and patients experienced severe side effects [132]. In a trial in non-small cell lung cancer, results were more positive, with two objective and 11 partial responses out of 33 patients. However, the unfavourable toxicity profile prevented the drug from moving into Phase III studies.

As no other, the story of BBR3464 demonstrates a great discrepancy between in vitro activity, tumour growth inhibition in xenograft models and clinical success. Gastrointestinal and haematological side effects observed in clinical trials were attributed to higher plasma protein binding in human in comparison to mice [133]. In conclusion, fast biotransformation and inactivation of BBR3464 was very likely a key reason of the disappointing results in clinical trials [3].

Liposomal formulations of cisplatin

As many drug candidates failed to achieve a positive benefit-risk balance due to systemic toxicity, researchers turned to targeted delivery of drugs directly to tumours. Passive drug delivery relies on enhanced permeability and retention (EPR) effect, i.e. better accumulation of macromolecules in tumour tissue because of its increased permeability and weak lymphatic clearance [3]. Upon expanding of the field, a number of drugs, and not only in oncology, were encapsulated into or linked to liposomes, micelles, nanoparticles and other macromolecules. One prominent example is the liposomal formulation of doxorubicin hydrochloride, which was approved by the FDA for treatment of ovarian cancer and AIDS-related Caposi's sarcoma in 2013 [134]. In contrast, active or carrier-based delivery aims at selective recognition of receptors on the surface of tumour cells and was expected to overcome defects in cellular accumulation responsible for drug resistance.

SPI-77 designed by Alza Pharmaceuticals, formerly Sequus Pharmaceuticals, contained cisplatin within stealth liposomes made from cholesterol, hydrogenated soy phosphatidylcholine and PEG-modified phosphatidylethanolamine (PEG = polyethylene glycol). With the drug-to-lipid ratio 1:70, the drug loading capacity was rather low [3]. A study in dogs bearing osteosarcoma compared SPI-77 with carboplatin. Out of 38 animals, nine were alive and disease-free, eight of them received the liposomal formulation and one got carboplatin. The authors reported this as a statistically significant difference with $p=0.02$. However, the relevance of this statistical evaluation is questionable. The advantage in disease-free survival was not convincing (156 days vs. 123 days in the SPI-77 and carboplatin group, respectively, $p=0.19$), as well as the difference in overall survival (333 days vs. 207 days in the SPI-77 and carboplatin group, respectively, $p=0.19$) [135]. In a Phase I trial in non-small cell lung cancer, only three of 17 patients achieved partial response upon treatment with SPI-77 / vinorelbin combination. Adverse effects were minimal; with neutropenia, dose-limiting toxicity was reached only at the highest dose evaluated upon dose escalation [136]. Chemoradiotherapy of head-and-neck cancer patients with the new liposomal formulation was not successful [137]. Following Phase II trials did not show more promising efficacy results. In one study in non-small cell lung cancer, the overall response rate was only 4.5 % [138]. In a similar trial in patients with recurrent and refractory disease, no responses were detected [139]. These findings were attributed to the low loading capacity and insufficient release of the free drug as was shown by low free platinum concentration in plasma and a lower degree of DNA platination in B16 melanoma tumour in mice [140].

Lipoplatin was developed by Regulon, Inc. as a liposomal formulation of cisplatin. The liposomes were 110 nm diameter and their shell consisted of soy phosphatidylcholine, cholesterol, dipalmitoyl phosphatidylglycerol (DPPG) and methoxy-PEG-distearoyl phosphatidylethanolamine. Its drug loading capacity of 1:10 was much higher than that of SPI-77. Upon preparation, first reverse micelles between DPPG and cisplatin were formed, these were later transferred to liposomes through interaction with neutral lipids. The drug product was a liposome suspension of 3 mg/ml cisplatin (as calculated for the free drug), which was stable for three years at 4 °C. The PEGylated coating increased the stability in body fluids, which was essential for drug extravasation into tumour tissue. Moreover, the anionic lipid DPPG was suggested to facilitate fusion of the liposomes with tumour cell membrane [141].

Lipoplatin exhibited much lower nephrotoxicity compared to cisplatin in mice and rats [142] and could be safely administered to dogs up to 150 mg/m^2 without intensive hydration [143]. In Phase I trials in patients who failed previous chemotherapy, only mild haematological and gastrointestinal toxicity and no other adverse effects were observed. This was attributed to the long circulation in the body (half-life in human plasma ca. 5 days compared to 6 h of cisplatin) and final accumulation in the tumour. Only three of 27 patients achieved partial response but 14 had stable disease with a clinical benefit of 2-5 months [144].

A Phase II dose escalation trial evaluated a combination of lipoplatin and gemcitabine in refractory patients with pancreatic cancer. In general, the regimen showed a favourable adverse effect profile. Grade 3 myelosuppression was observed only at the highest dose level. The efficacy data were similar to the above-mentioned Phase I study, out of 24 patients two (8.3 %) showed partial response and 14 (58.3 %) stable disease. This was considered a promising result given that the patients failed to respond to the prior therapy with gemcitabine [145]. In 2007, Regulon received an Orphan Designation for lipoplatin for treatment of pancreatic cancer (EU/3/07/451). The expected number of patients of 55,000 was in line with the definition of rare disease. The expected significant benefit was the availability of treatment for patients failing other therapies [146]. The registrational Phase II study in pancreatic cancer was underway and a randomised Phase III trial to compare lipoplatin / gemcitabine with placebo / gemcitabine was planned [141]. However, up to now there are no reports of these studies. It is possible that the unfavourable outcome prompted the company to discontinue development. Nevertheless, Orphan Designation remains active, as it is unclear whether lipoplatin still has a chance or not. For the sake of being comprehensive, trials in non-small cell lung cancer should be mentioned. A Phase II trial compared lipoplatin / gemcitabine with cisplatin / gemcitabine in 88 patients. The lipoplatin-based treatment was better tolerated, a significant reduction in nephrotoxicity ($p<0.001$) was achieved. The overall response rate in the lipoplatin arm was 31.7 % and in the cisplatin arm 25.6 %, however, the difference was not significant [147]. Nevertheless, these results encouraged setting up Phase III trials. One of them evaluated lipoplatin / gemcitabine vs. cisplatin / gemcitabine as first-line treatment having overall survival as a primary endpoint. An interim analysis was based on the data from 101 patients and showed a significant decrease in nausea/vomiting, nephro- and neurotoxicity [141]. However, no efficacy results of this study have ever been reported. Another study in non-small cell lung cancer compared lipoplatin and cisplatin, both in combination with paclitaxel. Upon termination of the study, 229 patients were evaluated. Again, a significant advantage of lipoplatin in terms of toxicity was observed but no improvement in overall survival or time to tumour progression was noted [141]. Apparently, since non-small cell lung cancer is often diagnosed at the late stage and characterised by high mortality rates and low life expectancy of patients, it is more important to achieve a breakthrough in efficacy rather than a milder toxicity profile, which likely explains the failure of lipoplatin in this tumour entity.

Discussion: what went wrong with new drug candidates

Drug development basically involves three stages: design and synthesis of the compound (normally to act on a particular target), preclinical evaluation and clinical development. After serendipitous discovery of cisplatin, researchers focused on the rational design of new platinum drug candidates. And indeed knowledge that cisplatin first undergoes hydrolysis to yield active species that also account for toxicity led to carboplatin as already described above. Platinum drugs target DNA, and a thorough characterisation of cisplatin-DNA adducts stimulated development of oxaliplatin and BBR3464 aiming at inducing different or no structural distortion on DNA. The idea to decrease reactivity towards cellular nucleophiles through the introduction of a bulky carrier ligand gave us picoplatin. The exploitation of the structural diversity offered by Pt(IV) complexes due to additional axial ligands resulted in the design of the first oral platinum drug satraplatin. Targeted delivery of cisplatin to tumour tissue was enabled by liposomal carriers of SPI-77 and lipoplatin. One can see that biochemical design produced a number of promising drug candidates.

Many more compounds, which are not described here but are extensively reviewed elsewhere [3], failed already at the preclinical stage. They were tested in cell lines and animal models and did not offer any particular advantage over approved platinum drugs. In vitro screening is often used to select promising compounds because it is cheap, fast and allows a high-throughput approach. However, cell line models only poorly reflect clinical setting. Exceptional cytotoxicity should not only be seen as a proof of anticancer activity but also of toxicity as the example of BBR3464 clearly shows (Table 4). Discerning antitumour and side effects would be enabled if testing in non-cancerous cell lines were run in parallel with that in tumour models. Closer attention should be given to candidates with moderate cytotoxicity like carboplatin. Instead of abandoning them, therapeutic windows should be defined in animal studies. As drug delivery systems are concerned, not only efficient targeting of the drug to the tumour but also drug release at the target site is of great importance as is clear from the story of SPI-77 (Table 4).

Table 4. Overview of factors resulting in regulatory failure of new platinum drug candidates (modified from [3]).

Drug	Furthest development stage	Failure reason(s)
BBR3464	Phase II	Toxicity due to fast protein binding
Satraplatin	Phase III	Lack of benefit in overall survival, composite endpoint of disease progression, wrong choice of tumour entity
Picoplatin	Phase III	Trial design flaws (choice of control group)
SPI-77	Phase II	Lack of efficacy due to low drug loading capacity and insufficient drug release
Lipoplatin	Phase II	Lack of efficacy (likely)

Animal models are already closer to human situation but transfer from the preclinical to clinical stage is not always successful. BBR3464 showed promising efficacy in mice, which allowed the compound to reach clinical trials despite high toxicity. But protein binding was higher in humans

and deactivation of the drug was faster. Moreover, the accepted level of toxicity in animal models goes up to 15 % body weight loss and up to 10 % lethality, which may lead to severe adverse effects in humans [132]. In clinical trials with BBR3464, dose reduction necessary to tolerate toxicity resulted in loss of efficacy. In animal studies, inhibition of tumour growth is assessed and is considered a sufficient proof of efficacy, whereas decrease in tumour lesions is crucial for therapeutic response in patients [3].

Clinical development deserves special attention since at the end the benefit-risk ratio, which is central to regulatory approval, depends on drug efficacy and its safety in humans. As cancer is a serious, life-threatening condition, efficacy may appear more important. And indeed, an analysis of NDAs in oncology that did not receive FDA approval between 2005 and 2015 (so including satraplatin) indicated that 2/3 (10 out 15 NDAs) failed due to efficacy reasons, and none of them because of safety problems [148]. However, one remembers that cisplatin could only be developed further after nephrotoxicity was under control. On the other hand, the requirements for efficacy may be higher nowadays than in 1970s. At present, we have numerous chemotherapies, targeted drugs and immunotherapies to treat various tumour entities, and a new drug needs to be superior to existing treatments in one way or another. This may be the reason that lipoplatin was not developed further as mentioned above. This thesis shows that in the dynamic field of drug development in oncology the state of the art and with that available therapies can change in the process of drug development. Approval of irinotecan for metastatic colorectal cancer undermined the first filing of oxaliplatin at the FDA. Appearance of docetaxel completely changed the situation in hormone-refractory prostate cancer and decreased chances of satraplatin to receive regulatory approval.

In order to demonstrate clinical benefit, clinical trial design should be appropriate. Out of 15 failed NDAs in the above-mentioned analysis, five (1/3) failed due to poor setup of clinical trials [148]. The first submission of oxaliplatin at the FDA failed to demonstrate an advantage in overall survival due to the limited power of clinical studies. Nowadays, the necessary number of patients to achieve a significant result is estimated already upon trial design. However, influence of external factors like post-study chemotherapy in a control group should be carefully controlled as shown by the example of picoplatin. In order to increase future revenues, drug developers sometimes aim at wider indication than offered by drug features. Satraplatin was developed as an oral drug and it might have been better to stick to that and to apply it in salvage setting against platinum-sensitive recurrent tumours, and not in refractory patients. As mentioned above, the results of a Phase II trial in ovarian cancer showed similar efficacy of satraplatin as compared to cisplatin and carboplatin. Even in this case, an oral drug could be preferable in the salvage therapy [3].

Current developments and outlook

As is clear from the above, platinum drugs form a cornerstone of modern chemotherapy of solid tumours. They are, however, seldom administered as a single agent. Already early clinical trials showed that drug combinations allow reducing the dose of each drug, and enhancing efficacy through synergistic interaction. Development of targeted drugs opened new possibilities as various inhibitors of EGFR (epidermal growth factor receptor) signalling appeared to potentiate anticancer activity of platinum drugs. But the results of clinical trials were mostly not encouraging. In non-small cell lung cancer, sorafenib incorporation into the standard carboplatin / paclitaxel regimen even enhanced mortality in patients with squamous cell carcinoma subtype [149]. A Phase II trial in urothelial cancer showed that gefitinib combined with cisplatin / gemcitabine did not bring any survival advantage [150]. However, gefitinib addition to the platinum-based therapy improved progression-free survival in non-small cell lung cancer patients featuring EGFR mutations [151].

DNA repair enzymes appear a more promising target for combination therapies with platinum drugs. Poly(ADP-ribose) polymerases (PARP) are crucial for the NER, therefore, PARP inhibitors like olaparib potentiate the effect of platinum drugs in a synergistic manner [3]. A synergistic interaction was noted in non-small cell lung cancer cell lines regardless of their p53 status [24]. A combination of olaparib with cisplatin-containing regimens was not well tolerated but showed promising activity in patients with BRCA1/2 (breast cancer 1 and 2, early onset genes) mutations in a Phase I trial [152]. Incorporation of veliparib that is being developed by AbbVie Inc. [153] into carboplatin / paclitaxel therapy in a randomised Phase II study showed a non-significant trend to improved survival of patients with advanced or metastatic non-small cell lung cancer. Interestingly, patients with squamous cell histology benefited the most [154]. For squamous NSCLC, veliparib received an Orphan Drug Designation from the FDA [155].

Interestingly, tumours with deficiency in homologous recombination, which is required for error-free closure of DNA duplex breaks formed upon base excision, demonstrate increased sensitivity to platinum complexes as well as to PARP inhibitors [6]. Such tumours are often characterised by deleterious mutations of BRCA1 and BRCA2 and can be identified using available diagnostic tools. Investigation of BRCA1/2 status is often warranted prior to the therapy with olaparib because it is authorised among others for advanced cancer of the ovaries, fallopian tubes and the peritoneum featuring BRCA1 and / or BRCA2 mutations. It would be worth investigation whether diagnostic screening of patients prior to administration of platinum drugs and subsequent personalisation of treatment can improve the efficacy of platinum-based chemotherapy.

Another promising approach is enhancing an apoptotic response to DNA damage induced by platinum drugs. AZD1775 developed by AstraZeneca [156] is an inhibitor of a WEE1 kinase, which regulates cell cycle by controlling a G2 checkpoint. The compound causes an escape from G2 cell cycle arrest and thereby from DNA repair. Moreover, this strategy is very fruitful in p53-deficient cells since they are characterised by a G1 checkpoint deficiency. In a Phase II proof-of-principle trial in p53-mutated ovarian cancer resistant or refractory to the 1st line platinum-based therapy, AZD1775 increased carboplatin efficacy thereby indicating the potential to overcome platinum drug resistance [157].

Platinum drugs form an indispensable basis of treatment of various solid tumours. We can learn a lot from their history, from serendipitous discovery of anticancer activity of cisplatin to the rational design and development of the second- and third-generation drugs. And although a regulatory approval of another platinum complex for an oncological indication is rather unlikely, astonishing efficacy and manageable toxicity profiles of cis-, carbo- and oxaliplatin will ensure their prominent role in the mainstream of cancer treatment for the decades to come. Moreover, combinations of novel therapies with the old “platinums” hold promise to improve survival of cancer patients and to ensure regulatory approval of newly developed treatments.

Summary

Before Barnett Rosenberg accidentally discovered cytostatic activity of cisplatin, being diagnosed with testicular cancer mostly meant a death penalty. Rosenberg had no intention to work with platinum, he aimed at studying the effect of an electric field on growth and division of bacteria. He used presumably inert platinum electrodes in his experiments. Having observed a halt in bacterial division, Rosenberg and his team pinned down the cause of the effect to the platinum complex formed upon the experimental conditions. It took some time and considerable effort to persuade the scientific community of the potential of the new drug candidate because the very idea to treat human beings with heavy metals appeared absurd. Nevertheless, cisplatin revolutionised the therapy of ovarian and testicular cancer, the latter having cure rates over 90 % nowadays. Such outstanding success but also drawbacks associated with cisplatin treatment, like severe side effects and development of resistance, stimulated search for new platinum-based drugs. Rational design and development finally led to regulatory approval of two other platinum complexes, carboplatin and oxaliplatin, all over the world. The former features clearly improved toxicity profile, whereas the latter demonstrates efficacy in colorectal cancer, which is intrinsically insensitive to cisplatin and carboplatin.

A number of other platinum drug candidates were evaluated in vitro, in animal models and some of them in clinical trials but none of them has received a worldwide approval. In this thesis, the reasons for the regulatory failure of several promising platinum compounds are analysed. These include too much focus on the exceptional cytotoxicity upon selection of drug candidates after in vitro screening, difficulties in transfer from the pre-clinical stage to the clinical benefit, flaws in clinical trial design, or wrong choice of the pursued indication. Constantly emerging new developments in the field of anticancer therapeutics also have a great impact on regulatory success. Although another platinum drug with a worldwide approval is not likely to be developed, combinations of the routinely used platinum-based drugs with novel therapies hold promise to greatly improve survival of cancer patients.

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