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CISPLATIN VERSUS CARBOPLATIN: COMPARATIVE REVIEW OF THERAPEUTIC MANAGEMENT IN SOLID MALIGNANCIES

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Highlights

- Platinum analogues, cisplatin and carboplatin, represent some of the most active cytotoxic agents in clinical oncology and are the backbone of most chemotherapeutic regimens.

- Despite relative similarities in mechanisms of action and activities, there are significant differences in both efficacy and toxicities for both platinum analogues in various malignancies.

- Carboplatin is a useful alternative in situations where cisplatin is contraindicated and this is not universally at the expense of efficacy.

- Platinum resistance, both de novo and acquired, is inevitable and understanding the mechanisms of resistance is essential in improving outcomes.

- Despite the burgeoning era of targeted therapies, the role of efficient DNA damaging agents such as platinum salts remains paramount especially in combination with these novel drugs.
Abstract

The platinum analogues, cisplatin and carboplatin, are among the most widely used chemotherapeutic agents in oncology. Both agents have a broad spectrum of clinical activity in numerous malignancies including gynaecological cancers, germ cell tumours, head and neck cancer, thoracic cancers and bladder cancer. Although the final mechanism of inducing tumour cell apoptosis is similar for both compounds, cisplatin has been shown to be more effective in treating specific tumour types. Whilst more favourable toxicity profiles are often associated with carboplatin, this can frequently translate to inferior response in certain malignancies. This review succinctly collates the evidence for the preferential use of these platinum analogues in particular settings in addition to the long-standing dilemma surrounding the paucity of biomarkers predicting response to these agents.

Keywords

cisplatin; carboplatin; radio-sensitisation; platinum-based chemotherapy; platinum resistance; platinum sensitivity
1. Introduction

Since the serendipitous discovery of the anti-neoplastic activity of cisplatin (cis-diammine-dichloroplatinum (II)) over 30 years ago[1], this agent alongside subsequent analogues (i.e. carboplatin, oxaliplatin, satraplatin) has become integral to the gold standard chemotherapeutic management of a myriad of malignancies including gynaecological, germ cell, head and neck, lung and bladder cancers. Cisplatin is the oldest member of this family with a well-recognised toxicity profile including emesis, renal dysfunction, neurotoxicity and ototoxicity. Carboplatin (cis-diammine-cyclobutanedicarboxylato-platinum (II)) was initially believed to have “comparable” therapeutic activity with cisplatin but is associated with significant myelotoxicity (particularly thrombocytopenia) but less nephrotoxicity and neurological sequelae. The mechanism key to their activity lies within the formation of DNA crosslinks which interrupts cellular DNA functioning and subsequently induces apoptosis [2]. Furthermore, they form covalent DNA adducts with other subcellular components such as proteins, lipids, RNA and mitochondrial RNA[3]. As the nomenclature infers, platinum is the core element of these two agents, with the key molecular difference centred on the leaving groups from the respective parent compounds; namely the chloride group for cisplatin and the cyclobutane-decarboxylate group for carboplatin[4].

The platinum (II) molecules exist in a planar structure in with the two amine groups and the two reactive “leaving” chloride (cisplatin) and cyclobutane-decarboxylate (carboplatin) groups existing in the same configuration (Figure 1) [4]. Moreover, the leaving groups are fixed in space in relation to the platinum core molecule and covalently bind DNA in an inflexible state. This DNA-platinum adduct can only be repaired by the nucleotide excision (NER) pathway [4]. The leaving groups also confer significant pharmacokinetic effects; with the cisplatin chloride groups readily dissociating in physiological pH conditions and the
carboplatin cyclobutane-decarboxylate groups requiring active cleavage by an esterase during intracellular dissociation. Hence, there are inherent differences in the intratumoural concentrations achieved with these drugs [5].

Indeed, previous in vitro studies with cisplatin treated hepatoma and transitional cell cancer cell lines highlighted diminished drug accumulation correlated with increasing resistance which is consequently determined by the activity of membrane drug transporters which mediate either active and passive influx of platinum ions [5]. Active influx of cisplatin appears to be ATP-ase dependent. Andrews et al. demonstrated up to 50% decrease of cisplatin uptake in both sensitive and resistant cells when these cells were pre-incubated with Na⁺/K⁺-ATPase-specific inhibitor [6]. Interestingly, both renal and cochlea cells, which are particularly susceptible to platinum induced trauma, express high levels of Na⁺/K⁺-ATPase. Multiple active uptake pathways, which facilitate the influx of platinum agents, have been identified in cells exhibiting platinum resistance. CTR1 (copper transporter 1, SLC31A1) is a 197 amino acids protein ubiquitously expressed transmembrane transporter involved in intracellular copper regulation. The extracellular terminus of the CTR1 transporter contains a methionine- and histidine- rich domain and CTR1 gene deletion has been shown to lower the intracellular platinum accumulation which inevitably promotes resistance [7].

Passive transporters have also been implicated in the cellular influx of cisplatin and carboplatin. The solute carrier (SLC) gene encodes a large family of passive transporters predominated by ion-coupled transporters and exchangers. These include the organic cation transporters (OCT) which are highly expressed in the proximal tubules of kidney and appear integral to the development of cisplatin-induced renal injury[5]. Interestingly, although OCT
is a principal cisplatin transporter, it appears to have negligible effects with carboplatin influx.

Inevitably, the net intracellular concentration of platinum is also determined by passive and active cellular efflux. Arguably the most significant membrane transporters in this realm include the ATP-binding cassette family (ABC) members (also known as multiple drug resistant protein 2; MRP2/P-glycoprotein), which orchestrate the regulation of cisplatin elimination and ensuing resistance [8]. It follows that cancer cells with decreased ABC transcript levels correlate with heightened platinum sensitivity. Other examples include the ATP7A/7B calcium and the glutathione conjugated (GS-X) efflux transporters, the latter of which is a component of the multiple drug resistant 1 (MDR1) family and down-regulation of these genes had been shown to cause intracellular cisplatin retention and subsequent resensitisation [9]. With respect to intracellular drug trafficking, preliminary studies using nucleic acid labelling and fluorescein-conjugated platinum complexes with elemental spectroscopies indicated that the platinum-compound concentration in cytoplasm appeared to be co-localised in vesicles such as lysosomes and melanosomes [5]. However, the mechanism of movement of the compound into the nucleus where the DNA damage takes place is unknown.

The ability of the cancer cells to repair DNA damage inflicted by cytotoxic agents is also an important factor in platinum sensitivity. Excision repair cross complementation group-1 (ERCC1)-XPF complex is a structure specific endonuclease that has a number of roles in DNA repair mechanisms including nucleotide excision repair, intra-strand crosslink repair and double strand break repair[10]. The role of ERCC1 in platinum resistance mechanism had been established in multiple ovarian cancer cell lines with intrinsic cisplatin resistance.[11]. Furthermore, ERCC1 mRNA expression may also be utilized to predict
response to platinum based regimens in treating non-small cell lung (NSCLC)[12, 13], gastric[14], cervical[15] and colorectal cancers[16]. However, the relationship between ERCC1 and patient outcomes appear less clear as data emanating from these studies either support or refute inverse correlations with ERCC1 expression and survival. Moreover, there is emerging evidence confirming no association between ERCC1 and platinum resistance in numerous tumour types including NSCLC [17] and ovarian cancer [18]. Nevertheless, the relationship between other mediators of DNA repair such as BRCA and response to platinum agents seemingly appears more consistent; whereby upregulation of BRCA1 (which mediates double strand break repair via homologous recombination) also induces platinum resistance [19] and conversely, BRCA mutations are a hallmark of platinum sensitivity [20]. The latter aspect is clearly exemplified by epithelial ovarian cancer in which at least 50% of cases harbour homologous recombination defects[21] which underpin the inherent platinum sensitivity of this disease at initial presentation.

In view of the fact that DNA adduct formation enhances radiosensitivity, platinum agents are paramount to a myriad of chemoradiation regimes in several tumour types. Several mechanisms have been postulated as to why platinum-radiation interactions facilitate tumour kill; e.g. inhibition of sublethal damage repair, inhibition of recovery from lethal damage, alterations in cellular kinetics and tumour volume leading to improved blood supply and increased tissue oxygenation [22]

Taking into consideration the potent apoptotic properties of platinum agents, it is clear to see why these drugs represent the cornerstone of management for numerous malignancies, which are described herein.
2. Non-small cell lung cancer (NSCLC)

Multiple trials with platinum containing regimens in NSCLC have shown superiority over best supportive care in term of improving overall survival [23]. Moreover, in the metastatic setting, 1st line therapy with a platinum doublet remains the gold standard of care. [24]. The question regarding the preference of platinum agents has been exhaustively addressed by a Cochrane review comparing the use of cisplatin and carboplatin in combination with third-generation drugs in advanced NSCLC. This meta-analysis concluded that although the use of cisplatin based regimes had higher response rates (HR 0.88; 95% CI 0.79-0.99), there was no difference overall survival (OS) outcome between the platinum agents.(HR 1.00; 95% CI 0.57-1.97)[25].

With the advent of the multi-folate antagonist, pemetrexed, as an active agent against non-squamous NSCLC, it has demonstrated superior efficacy and more favourable toxicity profile in combination with cisplatin compared with standard chemotherapy regimens in the 1st line setting [26]. Furthermore, a recent randomised phase II trial has compared pemetrexed in combination with cisplatin or carboplatin [27], with a median PFS of 6.0 and 4.7 months, and median OS of 11.7 & 8.9 months for cisplatin-pemetrexed and carboplatin-pemetrexed respectively. Although, this study was not designed and powered to compare the both arms of treatment, the overall efficacy and toxicity observed favoured the cisplatin-pemetrexed doublet.

Currently, there is no direct comparative study between cisplatin and carboplatin based regimes within in the neoadjuvant setting. However, there is evidence which confirms improved OS of operable stage III non-small cell lung cancer with platinum-based combinations [28]. Similarly, to date, there is no head to head comparison within the adjuvant
setting. Nevertheless a clear survival advantage has been established with both cisplatin and vinorelbine (stage IB, II and IIIA) and carboplatin /paclitaxel (stage I (T2 NO)) [29, 30].

3. Small-cell lung cancer (SCLC)

Carboplatin and cisplatin doublets are established treatment agents in both limited and extensive stage SCLC [31]. A recent meta-analysis of clinical studies based on individual patient data conducted by Rossi et al. compared the use of these two agents as 1st line treatment demonstrated no difference in efficacy but disparate toxicity profiles, with more myelotoxicity with carboplatin and higher rates of non-haematological toxicities with cisplatin [32]. Four randomised control trials with 663 patients included in the meta-analysis, which showed a median OS of 9.6 and 9.4 months for cisplatin and carboplatin respectively with a hazard ratio of 1.08 (95% CI 0.92-1.27) [32]. Similarly a descriptive study comparing the OS and locoregional control rates of SCLC patients receiving cisplatin-etoposide or carboplatin-etoposide showed median OS of 23 months versus 18 months (p = 0.10) in limited stage, 10 months vs 11 months (p=0.24) in extensive stage disease [33]and an overall 12 month locoregional control rate of 81% versus 61%.

4. Malignant mesothelioma

In malignant pleural mesothelioma, the combination of cisplatin and the multi-folate antagonist, pemetrexed, has been the cornerstone of first-line systemic therapy for the past decade [34]. This regimen proved superior to cisplatin monotherapy in terms of both OS (12.1 months vs 9.3 months) and ORR (41.3% vs 16.7%). Furthermore, phase II studies have demonstrated equivalent survival rates with carboplatin-pemetrexed doublets with (median
OS 12.7-14 months) [35-37]. These observations have been recapitulated in a multi-centre non-randomized platinum-pemetrexed study with 1704 chemo-naive subjects. Santoro et al. demonstrated similar 1-year survival (63.1% vs 64.0 %), median TTP (7.0 months vs 6.9 months) and marginally superior ORR (26.3% vs 21.7%) for cisplatin-pemetrexed and carboplatin-pemetrexed respectively[38].

5. Oesophageal and Gastric Cancer

In 1999, the RTOG 85-01 study established concurrent radiation with cisplatin/5-fluorouracil as definitive treatment for locally advanced oesophageal cancer. [39]. This regimen demonstrated significant median OS benefit compared to radiation (RT) alone (14 months vs 9 months) and a 5-year survival rate of 27%. However, in terms of neoadjuvant therapy, the role of platinum-based chemoradiation appears controversial. In patients with potentially resectable disease, the CROSS study confirmed a median OS advantage with carboplatin/paclitaxel and RT over surgery alone (49.4 months vs 24.0 months) alongside an approximate 30% pathological complete response rate [40]. Conversely, a neoadjuvant phase III study with cisplatin and 5-FU suggested that this approach was detrimental for stage I/II tumours [41]. To date, there are no comparative neoadjuvant chemoradiation studies with cisplatin and carboplatin.

With respect to neoadjuvant chemotherapy in gastro-oesophageal carcinoma, both MAGIC (epirubicin, cisplatin & 5-FU) and FNCLCC/FFCD (cisplatin & 5-FU) trials have established the benefits for cisplatin based regimens, with [42, 43]significant improvement of 5 year OS over surgery alone (34-36% vs 19-23%). Currently, there is a paucity of data to support the use of carboplatin-based regimens in this setting. In terms of metastatic oesophageal
squamous cell carcinoma, cisplatin has emerged as a key agent for systemic management. In a phase III study, Van Custem et al. reported ORR of 37% and 25% for docetaxel, cisplatin & 5-FU and cisplatin & 5-FU respectively[44]. Although a smaller phase II study with carboplatin and paclitaxel demonstrated an encouraging 43% ORR in 53 patients[45], cisplatin-based regimens remain the preferable option in the metastatic setting.

6. Germ cell tumours

Modern cisplatin based chemotherapy for metastatic germ cell tumours (GCT) in males has resulted in cure rates exceeding 80% [46]. Numerous attempts have been made to reduce treatment-associated toxicity of cisplatin-based regimens in these patients with excellent long-term prognosis. Hence, there has been a wealth of comparative studies aiming to investigate any potential non-inferiority with carboplatin. Horwich et al. conducted the largest of such studies in metastatic GCT [47] with 598 “good-risk” nonseminomatous GCT patients. Patients were randomized to receive four cycles of bleomycin, etoposide and cisplatin (BEP) (n=300) or bleomycin, etopside and carboplatin (CEB) (n=298) each at 21 day intervals. The results of this trial demonstrate significantly higher treatment failure rates in the CEB cohort compared with the BEP arm (79 vs 30 treatment failures p< 0.001), leading to failure free rates at 1 year of 77% (95% CI, 72%- 82%) and 91% (95% CI, 88% to 94%) respectively. In addition, there were significantly more deaths in the CEB arm compared to BEP (27 vs 10, p=0.003), translating to 3 year survival rates of 90% ( 95% CI, 86% to 94%) vs 97% ( 95% CI, 95% to 99%) [47].

Barjorin et al [48]conducted a multicentre, randomized phase III study evaluating the efficacy of 4 cycles of etoposide and cisplatin (EP) (n=134) versus 4 cycles of etoposide and carboplatin (EC) (n=131) in good-risk metastatic GCT as defined using Memorial Sloan
Kettering Cancer Center (MSKCC) criteria [49]. No significant differences were detected in complete response (CR) rates between EC (88%) and EP (90%). However 16 patients (12%) treated with EC relapsed from CR compared to only 4 (3%) treated with EP. Event-free and relapse-free survival were inferior for patients treated with EC (p=0.02 and 0.005 respectively) at a median follow up of 22.4 months but there was no statistically significant difference in OS. [48] Potential factors that may have adversely affected outcomes in the EC cohort include the four weekly cycling of EC and dosing methodology for carboplatin. The authors conducted exploratory analysis and failed to confirm a relationship between CR and AUC of the initial carboplatin dose [48].

Bokemeyer et al [50] conducted a subsequent study with 54 patients with metastatic non-seminomatous germ cell tumours and “minimal “ or “moderate” disease according to Indiana University criteria [51]. They were randomized to receive either 3 cycles of cisplatin, etoposide and bleomycin (PEB) (n=29) or 4 cycles of carboplatin, etoposide and bleomycin (CEB). Enrolment began in 1992 and the trial was terminated after an interim analysis of the first 54 patients revealed that patients in the CEB arm had an increased event rate. There was no significant difference in the CR rates (81% PEB, 76% CEB) and the median follow up was 33 months. Both relapse (32% vs 13%) and death rates (16% vs 3%) were higher for CEB compared with PEB and inevitably the higher negative event rate in the CEB arm reached statistical significance (p=0.03) [50]. This smaller trial does however suggest that even with current evidence based dosing of bleomycin and etoposide; carboplatin would appear inferior to cisplatin.

Carboplatin as a single agent has also been compared to cisplatin-based combination chemotherapy in metastatic seminoma given the superior prognosis of these patients compared with metastatic non-seminomatous counterparts[46]. With cure rates approaching 80-95%, the rationale again was to reduce the long term toxicity of cisplatin. Bokemeyer et
al. pooled and analysed data from 361 evaluable patients (181 cisplatin-based vs 177
carboplatin monotherapy) in two randomized phase III trials [52]. Patients treated with single
agent carboplatin had inferior 5-year PFS (72% and 92%; p<0.0001) and non-statistically
significant inferior OS (89% and 94%; p=0.090) compared to patients treated with cisplatin-
based combinations. Clearly, this is a comparison of a single agent versus a combination of
drugs all with proven efficacy and hence should be interpreted cautiously.

There is no available high quality randomised data in the adjuvant treatment of stage 1 or 2
testicular seminoma or non-seminoma directly comparing cisplatin to carboplatin. However,
with respect to paediatric extracranial malignant germ cell tumours, Hale et al [53] conducted
a retrospective analysis of 697 patients treated with either carboplatin in the UK and cisplatin
in the US and after adjustment for prognostic factors. Although there was no statistically
significant difference in the risk of failure, the nonrandomized nature of this data should be
interpreted cautiously. Similarly, there is no randomized comparative data on carboplatin
versus cisplatin in ovarian germ cell malignancies. To date, cisplatin based therapy remains
the gold standard [54]; however retrospective data has reported favourable outcomes with
carboplatin containing regimens [55].

7. Bladder cancer

There is emerging evidence supporting the use of neoadjuvant cisplatin- based chemotherapy
for locally advanced bladder carcinoma. A meta-analysis comparing this regimen followed by
local treatment versus local treatment alone pooled 3005 patients from 11 randomised
controlled trials [56]. This confirmed a significant OS advantage (HR = 0.86, 95% CI 0.77-
0.95, p = 0.003) equivalent to 5% absolute improvement in survival at 5 years with cisplatin-
based therapy. There is a paucity of convincing evidence to support the use of carboplatin in
the peri-operative setting and there are no comparative adjuvant studies to address any differential outcomes between cisplatin and carboplatin.

Within the metastatic setting, cisplatin-based regimens (i.e. cisplatin-gemcitabine (CG) or dose dense methotrexate, vinblastine, doxorubicin and cisplatin (DDMVAC) yet again represent the backbone of first line systemic management. [57, 58]. With respect to CG and classic MVAC, although both ORR (49% vs 46%) and OS (HR 1.04 [95% CI 0.82-1.32]) are equivalent, CG has a more favourable toxicity profile. [59]. Classical MVAC has since reported to be inferior to dose-dense MVAC in terms of ORR, PFS and CR rates[60]; however no head to head comparison has been made between CG and dose-dense MVAC. Despite this, Dogliotti et al. published a recent phase II comparative study comparing CG and carboplatin-gemcitabine confirmed ORR (49.1% vs 40.0%) and median OS (12.8 months vs 9.8 months) favouring cisplatin over carboplatin [61]. For chemo-naïve patients who are deemed cisplatin intolerant (i.e. GFR <30ml/min and or PS 2), Santis et al. conducted a comparative study with carboplatin-gemcitabine against a modified MVAC regimen consisting of methotrexate, vinblastine and carboplatin (M-CAVI)[62] with an ORR of 42% and 30% respectively. Another subsequent smaller study focused the use of carboplatin-gemcitabine in elderly or unfit patients where cisplatin was contraindicated. The 45.1% ORR and 20 month median OS reported in this trial certainly consolidates the notion that this regimen is a suitable alternative to cisplatin-based treatment in this patient cohort. [63].

8. Cancer of unknown primary (CUP)

As platinum salts exhibit a broad spectrum of activity in numerous solid malignancies, it appears fitting they represent the core of systemic management for carcinomas of unknown primary (CUP). The treatment of poorly differentiated CUP centres on carboplatin-based
regimens including carboplatin-gemcitabine, carboplatin-paclitaxel and carboplatin-docetaxel [64-66]. The carboplatin-paclitaxel doublet appears to be effective in patients with predominantly nodal and pleural based metastasis of unknown origin with 68.4% ORR and median OS of 15 months [64]. Interestingly, patients with liver, bone and multiple organs involvement gained limited benefit. These results are in stark contrast to subsequent phase II study utilising the same regimen which only garnered an ORR of 23% (95% CI 0.11-0.40) and median OS of 6.5 months (95% CI 5.5-10.1)[65]. However, in comparison to non-platinum based doublets such as gemcitabine-vinorelbine, carboplatin-paclitaxel remains superior in terms of both median OS (7.0 months vs 11.0 months) and 1-year survival rate (38% vs 29%) [66]. A comparative phase II study of carboplatin-docetaxel and cisplatin-docetaxel revealed that both regimens had similar response (22% vs 26%) and median OS rates (8 months for each arm). The carboplatin-docetaxel arm had a more favourable toxicity profile and a significant number of patients withdrew from the cisplatin-docetaxel doublet due to grade 3-4 emesis. [67]. Other studies have observed the efficacy and tolerability of platinum-gemcitabine regimens in CUP. With respect to carboplatin-gemcitabine, Pittmann et al. conducted a phase II study which reported a 30.5% ORR and median OS of 7.4 months [68]. Alongside the aforementioned study with metastatic urothelial cancer, this regimen was very well tolerated particularly in the elderly population. A separate French trial has shown a higher ORR (55%) but similar OS (8 months) with a cisplatin-gemcitabine doublet. [69, 70]. Of note, for SCC of unknown primary, historically, cisplatin based regimens in combination with 5-FU are often employed. Although there are no direct comparisons to 5-FU-cisplatin in this setting, this would certainly be an intuitive choice if cisplatin was contraindicated [71, 72].
9. Gynaecological cancers

In contrast to most other tumour types reviewed herein, carboplatin-doublets now represent the gold-standard of chemotherapeutic regimens for epithelial ovarian cancer (EOC) in neoadjuvant, adjuvant and palliative settings [73]. A number of pivotal studies have facilitated the establishment of this treatment paradigm. The largest of these was a non-inferiority phase III Gynaecologic Oncology Group (GOG) study (n=792) comparing carboplatin-paclitaxel with the then standard combination of cisplatin-paclitaxel for optimally debulked stage III EOC [74]. The authors reported equivalent median PFS (20.7 months vs 19.7 months) and OS (57.4 months vs 48.7 months) for carboplatin-paclitaxel and cisplatin-paclitaxel respectively [74]. The relative risk (RR) of progression for the carboplatin plus paclitaxel group was 0.88 (95% confidence interval [CI], 0.75 to 1.03) and the RR of death was 0.84 (95% CI, 0.70 to 1.02). Moreover, the carboplatin-doublet was better tolerated with significantly less renal and gastrointestinal toxicities. Although grade 4 leucopenia was more apparent with cisplatin, ≥ grade 2 thrombocytopenia was more frequently associated with the carboplatin arm. These observations have been recapitulated in a subsequent European study with superior quality of life associated with carboplatin-paclitaxel without any detriment to survival which was identical to cisplatin-paclitaxel [75]. However, in light of the confirmed benefits of intraperitoneal chemotherapy (i.p.) in patients with optimally debulked EOC [76], there has been a renaissance for cisplatin within the adjuvant sphere. For example, the landmark GOG 172 phase III study comparing i.p. versus i.v. cisplatin confirmed a marked improvement in median OS (65.6 months versus 49.7 months) and PFS (23.8 months versus 18.3 months) [77]. The benefit was evident despite a 68% drop-out rate from the i.p. arm which was associated with high rates of grade III/IV toxicities and poor quality of life up to 6 weeks post treatment. Intraperitoneal cisplatin and carboplatin treatment have been compared in a retrospective study as second-line palliative treatment which showed both non-inferiority
and similar toxicities[78]. With respect to more traditional first line i.v. administration for advanced EOC, a phase III randomised non-inferiority trial published in 2003 comparing the use of cisplatin-paclitaxel and carboplatin-paclitaxel showed a comparable proportion of patients without disease progression at 2 years (40.0% versus 37.5%) and similar PFS and OS rates [79]. Again, the use of carboplatin was shown to be associated with superior tolerability and quality of life.

In early stage cervical cancer, the GOG 120 study established the use of cisplatin based chemoradiation as the gold standard of therapy in patients with locally advanced disease [80]. This is further consolidated by the Green et al. 2001 meta-analysis of 19 randomized control trials of chemoradiation vs RT alone in which hazard ratios for both PFS and OS favoured chemoradiation with an absolute survival benefit of 12% at 5 years [81]. Although cisplatin appears to be the preferential radiosensitizer in this setting, carboplatin can be reserved for patients exhibiting significant toxicities with cisplatin or deemed to be at high risk of developing renal toxicity (i.e. diabetes, hypertension, >70 yrs) [82]. To date, there are no comparative studies of the radiosensitising effects of cisplatin and carboplatin. However, a small Phase I study in 24 patients with Stage IIIB disease treated with standard external bean radiation with 6 x weekly carboplatin exhibited equivalent response rates reported with cisplatin [83]...

Cisplatin is still regarded as the most active agent against cervical cancer in the metastatic setting. A phase III study conducted to compare the use of carboplatin-paclitaxel and cisplatin-paclitaxel in stage IV cervical cancer confirmed that these two regimens were statistically non-inferior to each other in OS (18.3 months versus 17.5 months with a hazard ratio of 0.99 90% CI 0.79-1.25)[84]. As with other trials, the carboplatin-paclitaxel doublet
had a more favourable toxicity profile. However, patients who were platinum naïve had a significantly better OS with cisplatin/paclitaxel [84].

In comparison with carboplatin, the use of cisplatin has been more extensively evaluated in the systemic management of endometrial cancer. A recent Cochrane review on chemotherapy for advanced, recurrent and metastatic disease identified 11 phase III studies and 80 phase II studies [85]. Seven of the 11 phase III studies were conducted to evaluate the effect of cisplatin in combination with other cytotoxic drugs including doxorubicin, paclitaxel, vinblastine, cyclophosphamide and methotrexate. The combination of cisplatin-doxorubicin demonstrated an ORR between 40% and 46% whilst cisplatin-based triple modality regimens achieved higher ORR up to 57% to 69% [85]. There was unfortunately a dearth of phase III data for carboplatin regimens. Twenty three of the 80 phase II studies were conducted using cisplatin monotherapy with an ORR varying widely between 4% to 42.3%. Only 5 phase II studies were identified to include the use of single agent carboplatin that showed response rates ranging from 28% to 33% and improvement of up to 61% when used in combination with paclitaxel [85]. These studies also highlighted the general preference for cisplatin in the first line setting for platinum naïve subjects [85]. In terms of metastatic disease, a phase II study was published in 2011 comparing 3 arms of treatments, which included cisplatin-docetaxel, carboplatin-docetaxel and carboplatin-paclitaxel [86]. It demonstrated ORRs of were 51.7%, 48.3% and 60.0% respectively with no significant difference in toxicity profiles. Moreover, this study highlighted a potential benefit in substituting cisplatin-based regimens for the carboplatin-paclitaxel doublet in this setting. Indeed, this concept is being further evaluated in the non-inferiority phase III GOG 209 study comparing carboplatin-paclitaxel versus cisplatin-doxorubicin-paclitaxel, which has widely been commonly adopted as a 1st line combinatorial regimen. There are early indications that carboplatin-paclitaxel
combination is not inferior in terms of response and survival and can be accepted as an appropriate cytotoxic backbone for future trials alongside targeted therapies [87].

10. Head and Neck Cancers

Concurrent treatment with high dose cisplatin and radiotherapy represents the definitive adjuvant treatment for high risk head and neck squamous cell carcinoma [88, 89]; with an associated complete response rate of 40% and median OS of 19.1 months. In comparison to radiation alone, the results from the two large phase III adjuvant studies confirm that the addition of cisplatin improves locoregional and disease free survival with mixed results on overall survival [89]. However, a separate EORTC study in 167 patients with local advanced head and neck cancer confirmed that both 5 year PFS (47% vs 36%) and OS (53% vs 40%; HR=0.70 (95% CI 0.52-0.95) favoured concurrent chemoradiotherapy over radiotherapy.)[90]. Moreover, a randomised non-inferiority trial comparing the use of single agent carboplatin against cisplatin as a radiosensitiser had successfully demonstrated similar survival outcomes [91]; with the reported 3 year OS was 79.2% and 77.7% respectively (p=0.9884, HR 0.83 95% CI 0.613-1.010) [91]. A more recent retrospective study demonstrated significant superiority of cisplatin to carboplatin in terms of adjuvant chemoradiotherapy for locally advanced oropharynx and oral cavity with a 3 year local control rate of 85% versus 62%, 3 year OS of 78% versus 51% and favourable toxicity profile [92]

For metastatic/recurrent head and neck cancers, 5-fluorouracil (5-FU) and platinum doublets are well-established standards of care. With respect to comparative studies, Forastiere et al. [93] published the results of a randomised study including 277 patients with advanced disease treated with single agent methotrexate or 5-FU either in combination carboplatin or cisplatin.
The reported ORR was 10%, 21% and 32% respectively but with no improvement in OS [93]. Interestingly, any survival benefits witnessed with combinatorial approaches over monotherapy has only recently been witnessed with the addition of the epidermal growth factor monoclonal antibody, cetuximab. Vermorken et al. published a phase III study randomised 220 of 442 eligible patients (with treatment naive metastatic/recurrent disease) to receive either carboplatin or cisplatin (based on investigators’ choice) with 5-fluorouracil with or without cetuximab. This trial demonstrated significant improvement in OS from 7.4 months with chemotherapy alone to 10.1 months with the addition of cetuximab [94]. Sixty four percent of the patients received cisplatin and the subgroup analysis showed greater benefit in term of PFS (HR 0.54 (95%CI 0.41-0.72) vs 0.50 (95%CI 0.35-0.72) and OS (HR 0.69 (95% CI 0.53-0.91) vs 0.98 (95% CI 0.69-1.41) in patients receiving cisplatin over carboplatin [94].

11. Conclusions

Although platinum salts remain the principal constituent amongst chemotherapeutic schedules for solid tumours, the landscape in managing these diseases has changed dramatically in the last decade. Clearly, this has been driven by the advent of targeted therapies and refinement of dosing regimens particularly in combination with other cytotoxic agents and radiation. Cisplatin and carboplatin remain the most commonly used platinum agents with the broadest spectrum of clinical activity. Comparatively, the evidence presented suggests that superior activity in terms of response rates, radiosensitisation and subsequent survival benefits is more evident with cisplatin. This is lucidly exemplified with germ cell tumours, cervical and head and neck carcinomas. However, the advantages over carboplatin
appear to be abrogated when cisplatin is combined with other cytotoxic agents such as paclitaxel, gemcitabine and pemetrexed in certain tumour types such as EOC and thoracic malignancies. Indeed, this is particularly highlighted with adjuvant and palliative treatment of EOC whereby, carboplatin represents the preferential platinum agent due equivalent biological activity alongside its’ superior toxicity profile. Although the myelosuppressive effects are well recognised, there is emerging evidence to confirming that this phenomenon can be circumvented when fractionated doses of carboplatin are combined with paclitaxel which induces platelet sparing effects [95]. Amongst most solid malignancies, the favourable non-haematological toxicity profile has undoubtedly promoted the use of carboplatin particularly in situations where cisplatin is contraindicated. It certain circumstances, this has facilitated treatment completion with well-sustained dose intensity to maximise the therapeutic potential of novel combinatorial agents. Nevertheless, it stands to reason that in the younger and fitter cohort of patients, particularly with germ cell tumours, cisplatin remains the paramount agent due to its irrefutable superior efficacy over carboplatin and the robustness of these patients to tolerate treatment.

Despite the similarities in the final cell killing mechanism and modes of acquired resistance, their differential pharmacokinetic properties alongside the intrinsic tolerance of normal host tissues to these agents significantly influences their respective efficacy. Ideally, genome wide association studies and pharmacogenetic studies may elucidate variants of germline genetic variations in each individual that are linked to platinum agents’ toxicities and their clinical efficacy. Indeed, there has been some progress in this area, with emerging evidence confirming that analysis of ERCC1 expression, BRCA mutations and homologous recombination defects maybe useful both prognostically and in predicting response to platinum based regimes [13, 14, 16, 21, 96]
However, the exploration of alternate biomarkers to predict platinum response is currently in nascent stages. *In vitro* studies have shown potential links between SULF2 methylation and high cofolin-1 level with cisplatin resistance and steroid receptor co-activator 3 (SRC3) expression with general platinum resistance in ovarian cancer [97-99]. Until such biomarkers are comprehensively validated and entrenched into daily oncology practice, the choice of platinum agents still remains at the discretion of the physician. Furthermore, the management decision should always factor patient performance status and intention of treatment alongside being guided by the evidence emanating from the aforementioned studies.

**CONFLICT OF INTEREST STATEMENT**

None to declare

**Conflict of interest statement**

The authors have no conflict of interests to declare.
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References


Figure Captions

Figure 1: Molecular structure of cisplatin and carboplatin
Figure 2: Major factors determining chemotherapeutic activity of platinum salts
# Table

Table 1: Summary of findings comparing the use of cisplatin and carboplatin in various tumour types.

<table>
<thead>
<tr>
<th>Tumour type</th>
<th>Cisplatin</th>
<th>Carboplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oesophageal and gastric cancer</td>
<td>Platinum agent of choice in combination with radiation as definitive and adjuvant therapy. Trimodality therapy with cisplatin is also the treatment of choice in the peri-operative and metastatic settings. No role for carboplatin – no established evidence to support its use.</td>
<td></td>
</tr>
<tr>
<td>Germ cell/testicular cancer</td>
<td>Cisplatin based chemotherapy regimens are the mainstay of treatment for high risk germ cell tumour. Role in salvage therapy currently under evaluation.</td>
<td>Single agent high dose carboplatin can be used as adjuvant therapy for low risk germ cell tumour. Emerging evidence to support the use of carboplatin as part of high dose chemotherapy in the salvage setting.</td>
</tr>
<tr>
<td>Bladder cancer</td>
<td>Well evaluated and established as the chemotherapeutic backbone agent in neoadjuvant and adjuvant settings. Platinum agent of choice in combination with gemcitabine in the metastatic setting. Inferior to cisplatin but some evidence to support carboplatin use in palliative settings in combination with gemcitabine in the elderly or those intolerant to cisplatin.</td>
<td></td>
</tr>
<tr>
<td>Cancer of unknown origin</td>
<td>No role due to toxicities in the management of adenocarcinoma of unknown origin. Limited data to support the use of cisplatin-carboplatin in metastatic squamous cell carcinoma of unknown origin.</td>
<td>Main choice of chemotherapy in combination with paclitaxel or gemcitabine. No role established in squamous cell carcinoma of unknown origin.</td>
</tr>
<tr>
<td>Gynaecological malignancies</td>
<td>Therapeutically equivalent to carboplatin but inferior in term of toxicities. Potential role as intra-peritoneal cytotoxic agent but this is not a universally established standard adjuvant regimen. Cisplatin is the primary radiosensitiser of choice in cervical cancer but its role in the metastatic setting is superseded by carboplatin. Cisplatin and doxorubicin is still recognized as a first line treatment option for metastatic uterine cancer but being increasingly substituted for carboplatin and paclitaxel.</td>
<td>Main choice of platinum agent in ovarian cancer treatment due to non-inferiority to cisplatin but better tolerability. Carboplatin and paclitaxel has been shown to be non-inferior and less toxic in comparison with cisplatin and paclitaxel in metastatic uterine cancer.</td>
</tr>
<tr>
<td>Head and neck cancer</td>
<td>High dose cisplatin with radiotherapy remains the treatment of choice for definitive and adjuvant therapy for head and neck cancer. Cisplatin and fluorouracil is the main combination regimen for metastatic head and neck squamous cell carcinoma.</td>
<td>Carboplatin is inferior to cisplatin as a radiosensitiser in head and neck cancers. Potential use of carboplatin to substitute cisplatin in the metastatic setting but considered to be inferior in combination with fluorouracil in terms of response, but no significant difference in overall survival.</td>
</tr>
</tbody>
</table>