**Overview: Platinum based chemotherapy ‘rechallenge’ in advanced non-ovarian solid malignancies**

**Key words:** cisplatin, carboplatin, resistance, chemotherapy, rechallenge

**Abstract**

Platinum-based chemotherapy (PBC) forms the backbone of treatment for many solid cancers, however resistance inevitably develops in those with advanced disease. Platinum rechallenge is a well-established concept in the management of ovarian cancer, small-cell lung cancer (SCLC) and germ cell tumours (GCT). In other solid malignancies there is a lack of quality evidence to support platinum rechallenge, yet it is a widely adopted strategy. Often, patients are within the last year of life, making questions of efficacy, treatment related toxicity and quality of life critical factors for treatment recommendations. In this overview we appraise the available evidence for platinum rechallenge and strategies being developed to attempt resensitisation of tumours to PBC.

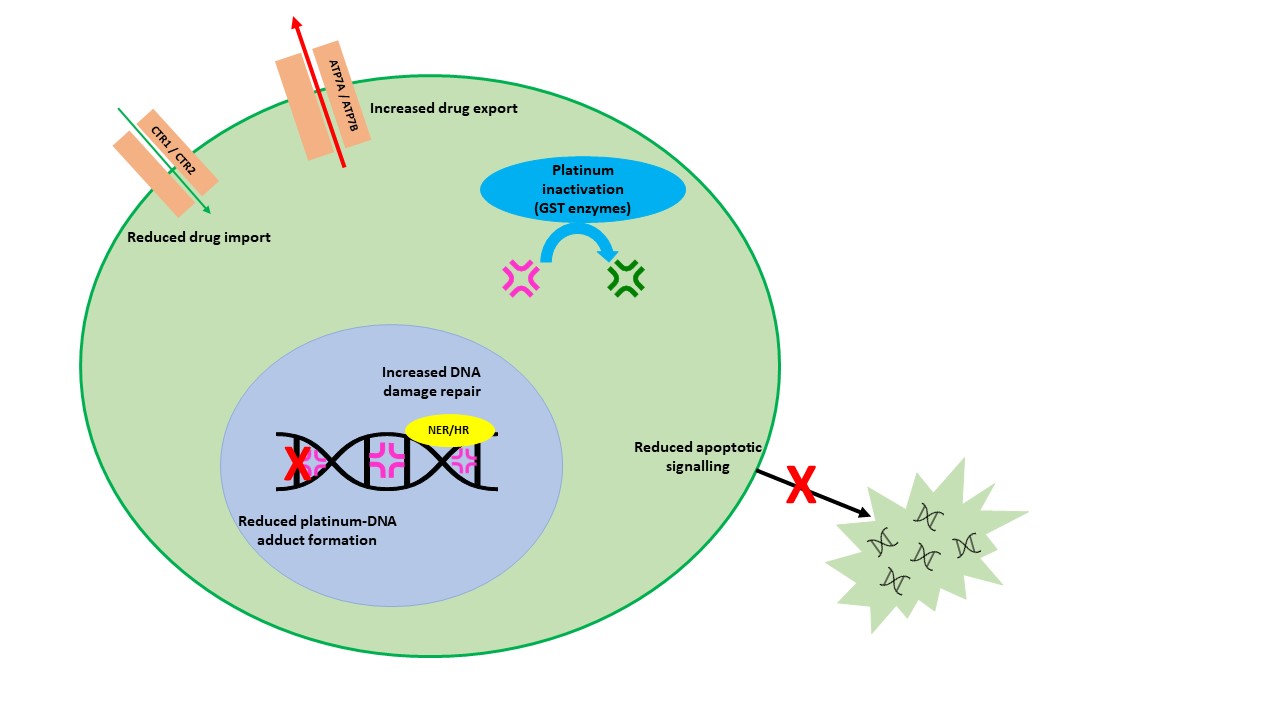
**Introduction**

PBC forms the backbone of treatment options for multiple solid malignancies. However, a platinum resistant phenotype inevitably develops in most patients with advanced disease. Effective treatment options for platinum-resistant advanced solid malignancies remain limited. As a result, patients are often retreated with PBC.

Platinum ‘rechallenge’ is a well-established concept in management of advanced ovarian cancer and small-cell lung cancer (SCLC). A key determinant of response is the platinum-free interval (PFI), with longer intervals associated with higher response rates and longer progression-free survival (PFS). Definitions of platinum sensitivity are not universally agreed and differ between tumour types. PBC regimens are also used as standard in relapsed or refractory GCTs, though the intent of treatment is usually curative[1]. In other solid malignancies data to support platinum rechallenge is limited and largely retrospective, non-randomised and often with small samples. These evidence limitations become important in the context of potential toxicity from PBC rechallenge and the substantial patient populations for whom this strategy might be utilised.

Cisplatin has multiple cytotoxic mechanisms of action, although the principal mechanism is formation of platinum-DNA adducts. Resulting intracellular adaptations to intracellular drug accumulation, intracellular drug detoxification, DNA damage repair and apoptotic signalling are key mechanisms of platinum resistance (see Figure 1)[2-4]. In addition to these ‘classical’ resistance mechanisms, recent data indicate other potential mechanisms including factors associated with the tumour microenvironment[2] and epigenetic changes[4, 5]. Several other molecular factors such as COX2, heat shock proteins, and various cell signalling molecules, are linked to platinum resistance in vitro, although most have not been verified in xenografts or clinically[5]. In a recent review a database of >900 genes potentially associated with platinum resistance was published[6]. In patients, there are likely to be multiple co-existing mechanisms of resistance, potentially linked to intra-tumoural heterogeneity, presenting significant challenges to developing strategies to reverse platinum resistance.

This overview summarises the evidence base, and its limitations, for PBC rechallenge, and strategies under development to reinstate platinum sensitivity. Cross-resistance between cisplatin and carboplatin is common. By comparison, cross-resistance between cisplatin/carboplatin and oxaliplatin is more variable[7]. Further discussion of ovarian cancer is beyond the scope of this review, but European guidelines and a comprehensive review on the management of recurrent ovarian cancer are available[8, 9].



**Figure 1: Mechanisms of platinum resistance.** A schematic representation of the major mechanisms of platinum resistance

**Urothelial carcinoma**

Outcomes for metastatic urothelial cancer (mUC) are poor with a median survival of 12 to 18 months[10]. Standard first-line treatment is cisplatin-based, in combination with gemcitabine (GC), or methotrexate, vinblastine and doxorubicin (MVAC), followed by maintenance avelumab immunotherapy[11, 12]. Carboplatin is substituted if cisplatin ‘ineligible’[12]. PD-1 directed immune checkpoint inhibitors (ICI) are the standard second-line treatment (if not receiving maintenance avelumab) following PBC. The FGFRinhibitor erdafitinib and the antibody-drug conjugate enfortumab vedotin are additional options in the platinum/ICI-refractory setting and have now been incorporated into European guidelines[12]. Subsequent progression is effectively inevitable, at which point treatment options are limited to further chemotherapy.

Non-platinum chemotherapy utilised for mUC following PBC and an ICI includes vinflunine and paclitaxel. However, there is no established survival advantage over best supportive care (BSC) alone, and in order to gain benefit patients need to be carefully selected[10]. There is little evidence to guide the decision between platinum-based and non-platinum-based regimens, with decisions usually made pragmatically based upon factors such as PFI, previous response and toxicity.

In a retrospective review of 296 patients who received subsequent chemotherapy for mUC after previous first-line PBC (fPBC) median overall survival (OS) following subsequent PBC (sPBC) was 7.9 months, compared to 5.5 months for subsequent non-PBC (snPBC) (hazard ratio (HR) 0.72, 95% CI 0.53-0.98, *p*=0.035). The sPBC group also had a superior disease control rate (DCR) of 57.4%, compared to 44.85% for the sNPBC group (*p*=0.041). The difference in median PFS for sPBC (4.1 months) and sNPBC (2.6 months) was not significant (HR 0.83, 95% CI 0.64 – 1.08, *p*=0.159). The treatment-free interval in the two groups was 4.4 and 2.2 months respectively[13]. Other data supporting platinum rechallenge in mUC, from a small retrospective analysis, showed that those treated with second-line GC (n=14) had a median OS of 9.6 months compared to 5.6 months in those that received non-GC second-line chemotherapy (n=37). The time to progression (TTP) was also superior at 4.0 months compared to 2.0 months[14].

Evidence is emerging to suggest that mUC response rates to PBC may be higher following ICI treatment. The optimal chemotherapy/immunotherapy sequence is yet to be fully established. A retrospective review of 12 patients receiving platinum rechallenge following ICI showed a relatively high objective response rate (ORR), PFS and OS of 66.7%, 7.9 months and 11.2 months respectively. Within this cohort, 4 patients who progressed following second-line platinum rechallenge subsequently responded to a further platinum rechallenge following ICI treatment[15]. This phenomenon is likely a result of neoantigen generation with chemotherapy and the transformation of ‘cold’ to ‘warm’ tumours[16].

Neoadjuvant PBC, usually GC, prior to radical cystectomy or chemoradiotherapy is standard care for muscle-invasive bladder cancer[10, 12]. For those relapsing following neoadjuvant chemotherapy, there is no formal consensus regarding whether further PBC, an alternative chemotherapy regimen, or an ICI, is optimal (although some data support an ICI if within one year). Regarding the chemotherapy selection aspect of this question, Locke et al performed a multicentre retrospective study of 145 patients receiving first-line chemotherapy for mUC following perioperative cisplatin-based chemotherapy. Use of cisplatin-based chemotherapy was associated with lower OS (HR 1.86, 95% CI 1.13-3.06, p=0.015) compared to non-cisplatin-based chemotherapy, particularly if relapsing ≤12 months from previous chemotherapy (HR 3.38, p=<0.001). However, cisplatin-based chemotherapy was not associated with worse PFS or response rates[17]. In a similar cohort of 41 patients given rechallenge PBC, those <52 weeks from perioperative therapy had an OS of 42 weeks, whilst those 52-104 weeks from perioperative therapy had OS of 70 weeks, suggesting use of rechallenge PBC chemotherapy may be reasonable if relapsing >12 months following perioperative chemotherapy[18]. Uncertainty remains regarding the optimal chemotherapy regimen for recurrent mUC after perioperative cisplatin-based chemotherapy limiting firm conclusions from the small data sets available.

**Oesophagogastric carcinoma**

PBC or chemoradiotherapy is the first-line neoadjuvant standard in oesophagogastric carcinoma, depending on tumour site and histology, whilst combination chemoimmunotherapy is first-line for metastatic or locally advanced oesophageal and HER2-negative gastro-oesophageal carcinoma (squamous cell (SCC) or adenocarcinoma). Prior to this PBC had been the first-line choice for many years. Previously the emphasis was on cisplatin-based treatment, though more recently oxaliplatin-based regimens have been incorporated into treatment pathways. Benefit from palliative chemotherapy is less clearly established in SCC than in adenocarcinoma, though generally patients receive platinum-based regimens if fit[19, 20].

Upon progression, treatment options include taxane, irinotecan or trifluridine-tipiracil chemotherapy (histology and tumour site dependent), however, survival gains are generally under 3 months compared to BSC[21-24]. Nivolumab is approved for advanced oesophageal SCC after fluropyrimidine- and PBC (if not receiving chemoimmunotherapy)[25]. Ramucirumab improves survival, alone or combined with paclitaxel, and is recommended in ESMO guidelines, though not by NICE in the UK[19, 26, 27].

A second-line phase II trial for advanced gastric cancer, following cisplatin combined with capecitabine or S1, randomised patients to docetaxel plus cisplatin (n=23), docetaxel plus S1 (n=23) or docetaxel alone (n=23). The study was halted approximately halfway through planned recruitment (through poor accrual) and did not detect a difference between arms in its primary endpoint of ORR (4.3%, 8.7% and 4.3% respectively). Docetaxel plus cisplatin had worse median OS compared to docetaxel alone (5.6 months vs. 10.0 months, p=0.035), although sample size limitations make it difficult to draw meaningful conclusions[28]. Other prospective trials of second-line chemotherapy involving platinum have not presented subgroup results to allow platinum rechallenge to be assessed[29].

A retrospective, single institution, review of 106 patients treated with sPBC for relapsed oesophagogastric cancer found median OS of 6.6 or 10 months for treatment with initial palliative or radical intent respectively. Median PFI was 10.7 and 15.5 months respectively, which is likely to have favourably influenced outcomes[30]. A smaller retrospective review included 39 patients treated with sPBC following progression after fPBC. Median PFI was 9.5 months. Median OS was 5.7 months, extending to 8 months in those responding to sPBC[31].

Accepting the substantial limitations of sample sizes and retrospective designs, these data support a hypothesis that PBC rechallenge may be a reasonable strategy in selected patients with longer PFI who remain fit for treatment. What is not clear from this data is the benefit of rechallenge with either single agent, or combination, PBC as all patients received combination regimens[30, 31].

**Biliary tract cancer**

Prognosis for advanced biliary tract cancer (aBTC) is poor with 5-year survival rates of approximately 5%[32]. GC is the standard first-line treatment[33]. ABC-06 was the first phase III study of second-line chemotherapy, following first-line GC, and established FOLFOX (leucovorin, fluorouracil, oxaliplatin) as the second-line standard. Median OS with FOLFOX plus active symptom control (ASC) was 6.2 months versus 5.3 months for ASC alone (HR 0·69 [95% CI 0·50–0·97]; p=0·031)[34].

Prior to ABC-06, data on second line options were limited to small phase II studies and retrospective reviews. A 2013 systematic review of 25 studies evaluated second-line chemotherapy in aBTC. Of fourteen phase II trials included, only three included platinum agents, and only one included platinum agents in both first- and second-line setting. The authors did not discuss the platinum rechallenge subset and therefore no conclusion can be drawn regarding this group. Median OS was 6.6 months for the phase II trial component of this review, which is likely influenced by better performance status of those receiving second-line chemotherapy, though this figure is supported by the results of ABC-06[35].

In a retrospective analysis of second-line chemotherapy for aBTC, 9 patients rechallenged with GC had a PFS to first-line GC of 11.2 months, which exceeded the 8.0 month PFS of the GC arm in the first line ABC-02 trial[33, 36]. Median PFS following GC rechallenge was 13.3 months, compared with 4.0 months in the FOLFOX plus ASC arm of ABC-06[34]. In the second-line chemotherapy cohort, 61% had locally advanced cancer, which may provide one driver towards relatively high PFS in the platinum rechallenge cohort. Interpretation of these results clearly requires caution in view of the very small sample size. Platinum rechallenge may be appropriate however in carefully selected patients and treatment interval may be one guiding factor.

**Non-small cell lung cancer (NSCLC)**

PBC is widely used for NSCLC. Cisplatin-based treatment is the standard for radical treatment. For palliative treatment, with no targetable gene alteration, patients are treated according to PD-L1 expression. If PD-L1 low, then typical first-line regimens include pembrolizumab, combined with carboplatin and paclitaxel for SCC, or carboplatin and pemetrexed for non-SCC. ICI monotherapy is typically used first-line if PD-L1 high, with platinum doublet chemotherapy upon progression, with pemetrexed for non-SCC, and gemcitabine or vinorelbine for SCC. Subsequent chemotherapy options upon progression after PBC are limited and include docetaxel, with or without nintedanib, for adenocarcinoma, and docetaxel monotherapy for SCC[37]. Median OS for docetaxel monotherapy lies between 5.7 to 9.1 months[38-40], whilst for adenocarcinoma histology median OS with docetaxel plus nintedanib was 12.6 months.[40] Despite addition of anti-angiogenic agents to chemotherapy in second-line and beyond, survival rates remain poor with an unmet need for improved treatments*.* Compared to SCLC there is limited data to support platinum rechallenge in NSCLC.

NVALT-07 was a randomised phase II trial of pemetrexed with or without carboplatin in 240 patients with advanced NSCLC progressing >3 months following first-line PBC. TTP was significantly longer in the combination arm (4.2 months) than pemetrexed alone (2.8 months; HR 0.67; 95% CI, 0.51 to 0.89; p=.005), though this did not translate into improvement in median OS (8 months and 7.6 months respectively)[41]. In the almost identical GOIRC 02-2006 trial there was no significant difference in response rate, PFS or OS between the 2 arms. Pooled analysis of both studies with 479 patients indicated that addition of carboplatin to pemetrexed resulted in no significant improvement in response rate (RR) (9% v 15%, 1.73, p=0.474), PFS (3.0 v 3.9 months, HR 0.86, p=0.119) or OS (8.2 v 8.7 months, HR 0.90, p=0.316) overall. However, for SCC, combining carboplatin with pemetrexed was associated with improved median OS from 5.4 to 9 months (HR 0.58, P interaction test =.039), presumably due to the relative lack of efficacy of pemetrexed in SCC[42]. In NVALT-07 25% had SCC compared to only 14.3% in GOIRC 02-2006 – enrolment of patients with SCC to GOIRC 02-2006 was halted part way through the study due to changes in the EMA pemetrexed label. Furthermore, NVALT-07 had higher response rates to first-line treatment and longer treatment-free intervals. Both factors may contribute to the divergent results between these studies[41, 42].

The pooled analysis of NVALT-07 and GOIRC 02-2006 was included within a meta-analysis of 11 studies, of 607 patients, with progressive disease following first-line platinum doublets, treated with second-line platinum doublets with taxanes or pemetrexed. Other studies included three phase II single-arm trials, four prospective series and two retrospective analyses. There was a high level of heterogeneity (I2 77.9%) so a random effects model was used for RR calculations. Overall RR was 27.5% and median PFS 3.9 months; but outcomes favoured taxane doublets (RR 37.8%, PFS 5.3 months) versus pemetrexed doublets (RR 22%, PFS 3.9 months; p<0.0001 both comparisons). Median OS was 8.7 months and not different with respect to platinum combination[43].

A later retrospective review assessed outcomes for 364 patients treated with second-line platinum doublets following first-line platinum-doublet chemotherapy. ORR was 11.5%. Median OS was 16 months in the overall population, 14 months in those with TTP of 0-3 months, and 25 months in those with TTP >12 months[44]. A median OS of 16 months is almost double that in NVALT-07 and GOIRC 02-2006 and perhaps surprising given the ORRs were similar and almost half had TTP of 0-3 months following initiation of first-line chemotherapy[44]. A small retrospective review of 22 NSCLC patients rechallenged with platinum plus gemcitabine following disease progression after >6 months showed a response rate of 15% and median OS of 10.4 months[45]. These figures are comparable to those of docetaxel monotherapy, though all patients had PFI of >6 months which is likely to have influenced outcomes. Data from further small retrospective studies is available in Table 1.

From the evidence presented, which is largely non-randomised and from small samples, it is difficult to form definitive conclusions regarding benefit of platinum rechallenge in NSCLC. Decisions should be made based on individual circumstance and consider factors such as PFI, prior response and other available treatments. All of the discussed studies occurred before routine use of first line pemetrexed and ICI adding difficulty in applying these results to the modern era.

In NSCLC, emerging evidence suggests improved response rates to subsequent chemotherapy following ICI treatment. A retrospective review of 73 patients showed an ORR of 66.7% for PBC after ICI compared to 39.5% for PBC before ICI. Corresponding ORRs for non-platinum chemotherapy were 46.9% and 25% respectively[46]. Results from other small retrospective studies support the finding of improved response rates after ICI with platinum-based and non-platinum-based regimes[47-51]. Prospective studies are needed to confirm these findings, ideally with randomised design, to optimise treatment sequencing in NSCLC.

**Mesothelioma**

PBC with cisplatin/carboplatin and pemetrexed, or combination ICI treatment with ipilimumab and nivolumab, are the first-line standards for mesothelioma[52]. Nivolumab is established as second-line treatment following the recent CONFIRM trial finding of a median OS of 10.9 months for nivolumab compared to 6.9 months for placebo (adjusted HR 0·69, 95% CI 0·52–0·91, p=0·0090)[53]. Prior to CONFIRM, retrospective analyses suggested a possible role for second-line PBC rechallenge. This may still be relevant for those unsuitable for an ICI, or who remain fit for systemic treatment following progression on an ICI.

Retrospective review of outcomes following second-line chemotherapy showed 52 patients re-treated with PBC achieved longer PFS (6.6 v 2.5 months, p<0.001) and OS (11.6 v 6.3 months, p=0.001) than those treated with non-platinum-based second-line chemotherapy[54]. In a further study, TTP in 21 patients receiving second-line platinum-pemetrexed chemotherapy was 5.7 months compared to 4.0 months for nine patients receiving pemetrexed alone[55]. With very small numbers it is difficult to make formal conclusions, but the available evidence suggests platinum rechallenge for progressive mesothelioma may be appropriate for selected patients.

**Head and neck cancer**

Platinum-based therapy is SOC treatment for the vast majority of head and neck SCC in the curative setting. Non-platinum-based treatments are recommended for those with recurrent disease within 6 months of PBC. If progression occurs > 6 months after PBC then recommended options include further PBC, or Pembrolizumab monotherapy in those with PD-L1-positive disease[56]. However, the population receiving platinum rechallenge has not been specifically studied. In a retrospective review of 45 patients receiving platinum rechallenge the DCR was 28.6% in those with a disease-free interval of ≥4.5 months compared to 54.8% for a disease-free interval of 54.8%[57]. Given the lack of evidence, the decision to rechallenge with PBC, particularly in those with a PFI < 6 months, needs to be carefully considered by the multidisciplinary team.

**Cervical and endometrial cancer**

Cisplatin and paclitaxel combined with bevacizumab is the preferred first-line regimen in metastatic or recurrent cervical SCC[58]. The GOG-240 trial that led to this recommendation showed that topotecan-paclitaxel was not superior to cisplatin–paclitaxel, even in those previously treated with cisplatin[59]. However, the efficacy of platinum rechallenge in cervical SCC has not been specifically studied. In the second-line setting multiple chemotherapy agents have shown poor response rates and ESMO guidelines make no formal recommendation[58], meaning treatment decisions must be made on an individual basis considering multiple factors.

Guidelines suggest further PBC can be considered in relapsed endometrial cancer >6 months after first-line carboplatin and paclitaxel, though this is largely based on anecdotal evidence[60].

**Small-cell lung cancer**

Platinum rechallenge is an established concept for SCLC, which is typically defined as ‘platinum-sensitive’ if the PFI is ≥3 months. Guidelines recommend rechallenge with platinum plus etoposide as an option in patients with platinum-sensitive disease[61, 62]. In an open-label randomised phase III trial, in 162 SCLC patients at progression >90 days following first line platinum plus etoposide, median PFS was 4.7 months for carboplatin plus etoposide versus 2.7 months for topotecan (HR 0.57, 90% CI 0.41-0.73, p=0.0041). Several other smaller studies also support the use of platinum rechallenge in platinum-sensitive SCLC (see Table 1). In those with a PFI <90 days, alternative chemotherapy such as topotecan or CAV (cyclophosphamide, doxorubicin and vincristine) is recommended if appropriate, though response rates are <15% and OS remains poor[63].

**Testicular germ cell tumours (GCT)**

PBC regimens are standard treatment in the first-line and relapsed settings for GCTs[1, 64]. Definitions of platinum sensitivity differ from those associated with ovarian cancer and SCLC. Uniquely, GCT tends to be defined as platinum-sensitive if at least stable disease is achieved for >4 weeks after the last chemotherapy course, and platinum-refractory if disease progression occurs <4 weeks[65-68]. Reflecting the rare setting, conclusive recommendations cannot be made about the optimal initial salvage approach for relapsed or refractory GCT. However, both conventional-dose and high-dose chemotherapy is platinum-based. Tables 2-4 summarise studies in this area. Chemotherapy following high-dose chemotherapy is usually gemcitabine with oxaliplatin and/or paclitaxel[1]. In this setting long-term survival is achieved in only 10-15%[69] and there remains a need for more effective treatments. In the first trial of ICI in refractory GCT single-agent pembrolizumab did not appear to have clinically meaningful activity[70].

**Strategies to overcome platinum resistance**

Targeting a single resistance mechanism may be inadequate for chemosensitisation. Novel combination strategies are likely to be the most successful way of circumventing platinum resistance with promising recent developments, particularly in targeting epigenetic resistance mechanisms. DNA methyltransferase inhibitors (DNMTi) have been combined with PBC in early phase clinical trials with some success. A phase II trial of the DNMTi guadecitabine in combination with carboplatin for platinum-resistant recurrent ovarian cancer did not meet its PFS primary endpoint despite an intriguing trend in favour of the DNMTi/platinum combination arm (median PFS 16.3 versus 9.1 weeks, p=0.07). However, the 6-month progression-free rate (secondary endpoint) was significantly higher in the guadecitabine/carboplatin group (37% versus 11%; p=0.003)[71]. The phase Ib/IIa SPIRE trial defined a safe dose and schedule of guadecitabine in combination with GC for solid cancers. Although not designed to formally assess clinical efficacy, clinical benefit was seen in some patients with multiply pre-treated, platinum-resistant, GCT [72].

Transport of platinum agents into cells occurs via copper transport proteins, namely CTR1. In preclinical studies copper-lowering agents resensitised platinum-resistant tumour cells to platinum therapy through upregulated expression of CTR1 and enhanced platinum uptake. A subsequent phase 1 trial of carboplatin combined with the copper-lowering agent trientine showed promising evidence of anti-tumour activity warranting further investigation[73]. Cisplatin is transported out of cells by the copper transport protein ATP7B, and increased ATP7B expression is associated with cisplatin resistance[3]. Subsequent data found nano-liposomal administered ATP7B siRNA combined with cisplatin was highly effective at reducing tumour growth in ovarian carcinoma mouse models[74, 75].

Aurora kinases are integral to mitosis and the cell cycle and overexpressed in many epithelial ovarian cancers. Aurora-A kinase has also been implicated in protecting cells from apoptosis induced by chemotherapy agents, including cisplatin. Combining the pan-Aurora kinase inhibitor MK-0457 with cisplatin significantly reduced tumour growth and metastasis versus cisplatin alone in ovarian carcinoma mouse models[75, 76].

These examples demonstrate promising avenues for reversing platinum resistance. However, the multifactorial nature of platinum resistance remains a significant challenge and further work is needed. We will almost certainly require predictive biomarkers for potential resistance reversal strategies to be optimally deployed.

**Conclusion**

Platinum rechallenge is commonly utilised across multiple cancers, with emerging evidence to suggest its efficacy in NSCLC and mUC, in addition to its established role in ovarian cancer, SCLC and GCT. Often, patients are within the last year of life, making questions of efficacy, treatment related toxicity and quality of life critical factors for treatment recommendations. Evidence discussed in this review supports a role for PBC rechallenge in advanced solid malignancies. However, in virtually every setting, there are substantial limitations to the quality of the evidence base relating to small sample sizes, lack of randomisation, retrospective data sets and a virtually complete absence of quality of life or toxicity data. Pragmatic decisions need to be made based on individual circumstance, with open discussion between oncologists and their patients about the aims, and realistic exceptions, of platinum rechallenge. Immunotherapy has changed treatment paradigms for many cancers and how it works in combination with chemotherapy and other treatments such as PARP inhibitors is of great interest. Retrospective evidence suggests that response rates to platinum rechallenge may improve following an ICI. This should be assessed formally in clinical trials however, bearing in mind the potential for bias in current data. Strategies are being developed to attempt resensitisation of tumours to PBC, including tumoural epigenetic reprogramming. Finally, predictive biomarkers of sensitivity to platinum rechallenge are largely lacking beyond, often ill defined, concepts of PFI, prior platinum response and performance status. Prospective study of molecular markers for treatment benefit would be of significant value.

**Table 1: Survival and response rates for platinum rechallenge in solid cancers**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| *Paper* | *Primary tumour* | *Type* | *Number patients (platinum arm)* | *Platinum agent used* | *Response rate (in platinum group)* | *PFS in months* | *OS in months – from time of rechallenge* | *Comments/notes* |
| Wong et al 2021 [13] | Urothelial | Retrospective review | 296 | Platinum doublet | 30.4%  (DCR 57.4%) | 4.1 | 7.9 | Platinum versus non-platinum 2nd line ChT |
| Locke et al  2016 [17] | Urothelial | Retrospective review | 145 | Cisplatin or non-cisplatin based | 36.3%  (DCR 54%) | 6.0 (5.5 – 7.4) | 18.0  (13.8 – 21.4)  **See comments** | **1st line** chemo for advanced urothelial cancer after perioperative cisplatin |
| Necchi et al 2015 [18] | Urothelial | Retrospective review | 41 | Cisplatin-based | 51.2% | 7.0 | 15.6 months  **See comments** | **1st line** chemo for advanced urothelial cancer after perioperative cisplatin |
| Tsang et al 2019 [14] | Urothelial | Retrospective review | 14 | Cisplatin & gemcitabine | Not available | 4.0 | 9.6 | 12 has 1st line Cisplatin-Gemcitabine, 1 had MVAC, 1 had ‘other’ |
| Gravis et al 2018 [15] | Urothelial | Retrospective review | 12 | Platinum-based | 66.7% | 7.9 (2.0 – 20.1) | 11.2 (2.2 – 20.1) | Rechallenge after immunotherapy |
| Okines et al 2010 [30] | OG | Retrospective review | 106 | Platinum-Fluoropyrimidine +/- epirubicin. | Initial radical intent: 27% (DCR 69%)  Initial pall intent: 24% (DCR 54%) | 5.1 (3.5 – 6.8) for initial radical intent  3.9 (2.1 – 5.8) for initial palliative intent | 10 (7.3 – 12.6) for initial radical intent  6.6 (3.9 – 9.3) for initial palliative intent | Only include if progressed >3months after 1st line platinum-based chemotherapy. |
| Hingorani et al 2015 [31] | OG | Retrospective review | 39 | Mixture of regimes | <6m interval: 33%  6-12m: 47%  >12m: 90% | 3 (2.0 – 4.0) | 5.7 (4.7 – 6.7) | Response independent of time interval since completion of 1st line treatment and of platinum agent used. |
| Lee et al 2017 [28] | Gastric | Phase II trial | 23 | Docetaxel & cisplatin | 4.3% (further 8.7% with unconfirmed PR) | 1.8 (0.8-2.9) | 5.6 (4.4-6.7) | Compared to Docetaxel alone or Docetaxel + S1, following 1st line cisplatin based ChT (with S1 or Cape) |
| Adhikaree 2014 [36] | Biliary | Retrospective review | 9 | Cisplatin & gemcitabine | 3/9 | 13.3 | 26.7  (from consideration of palliative chemo) | Definition of OS unclear |
| Rambeau et al 2019 [57] | H&N | Retrospective review | 45 | Platinum, Cetuximab + 5FU/Docetaxel | 28.8% (inc 4.4% CR)  (DCR 40%) | 3.0 (2.3 – 4.6) | 5.0 (3.7 – 8.0) | Previously treated with chemoradiotherapy |
| Petrelli et al 2013 [43] | NSCLC | Meta-analysis (11) | 591 | Platinum & pemetrexed/ docetaxel | 27.5% | 3.9 (2.3 – 6.43) | 8.7 (8.0 – 17.4) | Platinum in combination with pemetrexed or docetaxel |
| Mo et al 2016 [44] | NSCLC | Retrospective review | 364 | Not specified | 0-3 month PFI: 10.6%  4-6m: 8.5%  7-12m: 18.3%  >12m: 12.9% | 3 (2.3 – 3.7) | 16 (13.5 – 18.5) | Platinum agents used not specified.  Response rates is CR+PR combined. |
| Smit et al 2009 [41] | NSCLC | Phase II trial  **\*Included in Petrelli meta-analysis** | 119 | Pemetrexed- carboplatin  (versus pemetrexed) | ORR 9% (PR rate 17% | 4.2 (3.7 v 4.6) | 8 (7.4 – 10.5) | None received pemetrexed in 1st line setting  \*Included in Petrelli meta-analysis |
| Ardizzoni et al [42] | NSCLC | Phase II trial  **\*Included in Petrelli meta-analysis** | 119 | Pemetrexed- carboplatin (versus pemetrexed) | 12.5% | 3.5 (2.9-4.7) | 9.2 (6.9 -11.6) | None received pemetrexed in 1st line setting  \*Included in Petrelli meta-analysis |
| Nagano et al 2010 [77] | NSCLC | Retrospective review | 28 (2/28 had non platinum rechallenge) | Platinum doublet | 29% | Not available | 17.0 | 2 of the patients in ‘rechallenge’ group had non-platinum based treatment |
| Imai et al 2015 [78] | NSCLC | Retrospective review | 24 | Platinum combination | 16.7%  (DCR 58.3%) | 4.2 | 16.5 | All previously treated with CRT. |
| Khan et al 2013 [45] | NSCLC | Retrospective review | 22 | Carboplatin & gemcitabine | 15%  (DCR 75%) | 5.6 | 10.4 | All received Gemcitabine & platinum in 1st line setting |
| Zucali et al 2012 [54] | Mesothelioma | Retrospective review | 52 | Platinum doublet | DCR 70.6% | 6.6 | 11.6 | Platinum agent used not specified |
| Bearz et al 2012[55] | Mesothelioma | Retrospective review | 21 | Platinum & pemetrexed | Not available | 5.7 (4.0 in pemetrexed alone group) | Not available. | ORR and OS only available for entire cohort (incl pemetrexed alone) |
| Garassino et al 2011 [79] | SCLC | Retrospective review | 161 | ‘Platinum based’ | 34.5% | Only available for plat & non-plat combined | Only available for plat & non-plat combined | Includes those with platinum-sensitive & platinum-refractory disease |
| Korkmaz et al 2013 [80] | SCLC | Retrospective review | 120 | Platinum & etoposide | 55% | 6.2 | 11.4 | Data is for those with platinum-sensitive relapse (>90 days) |
| Tendler et al 2019 [81] | SCLC | Retrospective review | 90  44 | Platinum doublet | Not available | Extensive disease  3.7 (3.2 – 4.3)  Limited disease  4.8 (3.7 – 6.1) | 5.2 (4.3 – 6.7)  9.0 (6.8 – 11.5) | Impact of platinum-free interval not clear. |
| Genestreti et al 2015 [82] | SCLC | Retrospective review | 112 | Carboplatin & etoposide | 45% (incl 3% CR) | 5.5 (4.4 – 6.3) | 7.9 (6.9 – 9.7) | Data is for those with platinum-sensitive relapse (>90 days) |
| Goto et al 2016 [83] | SCLC | Phase III trial | 90 | Cisplatin, etoposide & irinotecan | 84% (75-91) | 5.7 (5.2-6.2) | 18.2 (15.7 – 20.6) | Data is for those with platinum-sensitive relapse (>90 days)  Topotecan control arm |
| Baize et al  2020 [84] | SCLC | Phase III trial | 82 | Carboplatin & etoposide | 49% (41 – 55) | 4.7 (3.9 – 5.5) | 7.5 (5.4 – 9.5) | Data is for those with platinum-sensitive relapse (>90 days) |
| Naito et al 2018 [85] | SCLC | Retrospective review | 67 | Platinum doublet (with irinotecan or etoposide) | ORR 52.2% (DCR 82.1%) | 5.1 (4.3 – 5.4) | 10.8 (8.7 – 14.5) | Data is for those with platinum-sensitive relapse (>90 days) |
| Miura et al 2018[86] | SCLC | Retrospective review | 37 (2nd line)  25 (3rd line) | Platinum doublet | ORR 59.5%  ORR 47.8% | Not available | Not available | Data is for those with platinum-sensitive relapse  (not explicitly stated as >90 days) |
| Steffens et al 2019 [87] | SCLC | Prospective cohort | 31 | Platinum & etoposide | 38.7% | 4.5 (2.9 – 10.2) | 8.0 (6.8 – 16.5) | Median TFI was 4.2 months |
| Inoue et al 2015[88] | SCLC | Phase II trial | 30 | Platinum doublet (etoposide or irinotecan) | 43% (28-58) | 5.1 | 14.3 | Data is for those with platinum-sensitive relapse (>90 days).  Amrubicin control arm. |
| Wakuda et al 2019 [89] | SCLC | Retrospective review | 27 | Platinum doublet – not specified | 48% | 5.5 (3.4 – 6.1) | 14.2 (6.4 – 25.6) | Data is for those with platinum-sensitive relapse (>90 days) |
| Shiozawa et al 2018 [90] | SCLC | Retrospective review | 20 | Platinum & etoposide | Not available | 4.5 (3.5 – 5.4) | 10.5 (7.9 – 13.0) | Data is for those with platinum-sensitive relapse (>90 days) |
| Wakuda et al 2015 [91] | SCLC | Retrospective review | 19 | 68% platinum-etoposide, 32% cisplatin-irinotecan. | ORR 37% (46% in those with TFI >180 days) | 5.6 | 14.4 | Data is for those with platinum-sensitive relapse (>90 days) |

ChT, chemotherapy; DCR, disease control rate; PR, partial response; CR, complete response; ORR, objective response rate; PFI, platinum-free interval; TFI, treatment-free interval; CRT, chemoradiotherapy.

**Table 2: Survival and response rates for platinum rechallenge in testicular GCT – initial salvage with conventional dose chemotherapy**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| *Paper* | *Primary tumour* | *Type* | *Number patients (platinum retreat)* | *Regime*  *(2nd line)* | *RR* | *PFS in months* | *OS in months – from time of rechallenge* | *Comments/notes* |
| Loehrer et al 1998 [92] | Primary refractory GCT | Phase II trial | 135 | VeIP | CR 49.6% | Not available | Durable CR 23.7% | Primary refractory disease |
| Pico et al 2005 [93] | Relapsed GCT | Phase III trial | 122 | VeIP/VIP (control arm) | 31% | 3year EFS 35% | 47% (median follow-up 45m) | No benefit to addition of HDCT in experimental arm |
| McCaffrey 1997 [94] | Relapsed GCT | Retrospective review | 56 | VIP/VeIP | CR 36% | Not available | 23% | Mix of complete and incomplete response to 1st line chemo |
| Kondagunta et al 2005 [95] | Relapsed GCT | Prospective trial | 46 | TIP (Paclitaxel, Ifos, Cisplatin) | CR 70% | 2 year PFS 65% | Durable CR 63% (at 69m) | All had favourable features |
| Mead et al 2005 [96] | Relapsed GCT | Phase II trial | 43 | TIP | CR 19%  ORR 60%  FRR: 72% | 1year failure free survival 36% | 1 year OS 70% | Includes all relapse intervals and all primary sites  Lower dose Paclitaxel |
| Mardiak et al 2005 - [97] | Relapsed GCT | Phase II trial | 17 | TIP | CR 41% | 2 year DFS 47% | 2 year OS 64% | Included late relapse and non-testicular primary |
| Kurobe et al 2014 [98] | Relapsed/refractory GCT | Retrospective review | 16 | TIP | 17% (refractory disease)  50% (relapsed disease) | Not available | 5y OS 66% (relapsed disease) and 33% (refractory disease) | 16 patients (11 with relapsed disease and five with refractory disease) |

CR, complete response; ORR, objective response rate; DFS, disease-free survival; FRR, favourable response rate; PFS, progression-free survival; OS, overall survival

**Table 3: Survival and response rates for platinum rechallenge in testicular GCT – salvage with high dose chemotherapy (HDCT)**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| *Paper* | *Primary tumour* | *Type* | *Number patients (platinum retreat)* | *Regime* | *RR* | *PFS in months* | *OS in months – from time of rechallenge* | *Comments/notes* |
| Lorch et al 2011 [99] | Relapsed GCT | Retrospective review | 821 | Variety HDCT regimens | Not available | 2yr PFS 49.6% | 5yr OS 53.2% | Regimens all involved carboplatin & etoposide +/- other agents |
| Adra et al 2016 [100] | Relapsed GCT | Retrospective review | 364 | Carboplatin + etoposide (x2) | Not available | 2yr PFS 60% | 2yr OS 66% | 83% having HDCT as initial salvage  Excluded late relapse |
| Einhorn et al 2007 [65] | Relapsed GCT | Retrospective review | 184 | Carboplatin & etoposide + autologous stem cell return | Not available | 63% DFS (with median follow-up of 48 months) | Not available | 73% having HDCT as initial salvage |
| Pico et al 2005 [93] | Relapsed GCT | Randomised phase III | 125 | VIP (x3) + CarboPEC & stem cell return | Overall CR 43% | 3year EFS 42% | 47% (median follow-up 45m) | No benefit to addition of HDCT in experimental arm |
| Lorch et al 2012 [101] | Relapsed GCT | Randomised phase III trial | 108 | \*VIP (x1) + high-dose carboplatin & etoposide (x3)  \*VIP (x3) + high-dose carboplatin, etoposide & cyclophosphamide (x1) | Not available | 2yr PFS 52%  2yr PFS 47% | 5yr OS 50%  5yr OS 40% | Includes those with platinum-refractory disease – proportion unclear.  Includes those who had previous salvage treatment (14-15%) |
| Feldman et all 2010 [67] | Relapsed GCT | Phase I/II trial | 104 | TI-CE + stem cell return | CR 50%  Best response 58% | 5yr DFS 47% | 5yr OS 52% | 76% having HDCT as initial salvage |
| Kondagunta et al 2007 [102] | Relapsed/refractory GCT | Phase I (to find Carboplatin dose)/phase II | 47 | TICE + stem cell return | CR 49% (55% CR to chemo + surgery) | 40 month DFS: 51% |  | 79% had refractory disease following previous platinum-based regime. |
| Motzer et al 2000 [103] | Relapsed & refractoryGCT | Phase I/phase II | 37 | TICE + stem cell return | CR 57% | DFS 49% at median follow-up of 31 months | 54% at median follow-up of 31 months | All had ‘cisplatin-resistant’ disease |
| Margolin et al 2005 [104] | Relapsed or refractory GCT | Phase II trial | 33 | Carboplatin, Paclitaxel + Ifosfamide/Etoposide | N/A | 36% at median follow-up of 67 months | Figures not available | Mix of relapsed and refractory. 64% had increasing markers at time of entry |

CR, complete response; DFS, disease-free survival; EFS, event free survival; PFS, progression-free survival; OS, overall survival

**Table 4: Survival and response rates for platinum-refractory testicular GCT – subsequent salvage treatment following HDCT**

ORR, objective response rate; CR, complete response; PFS, progression-free survival; OS, overall survival

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| *Paper* | *Primary tumour* | *Type* | *Number patients* | *Regime* | *RR* | *PFS in months* | *OS in months – from time of rechallenge* | *Comments/notes* |
| Porcu et al 2000 [105] | Relapsed /refractory GCT | Retrospective review | 47 | Variety | ORR 18.2%  CR 6% | Not available | 11 (48 weeks) | All had relapsed following HDCT + stem cells |
| Bokemeyer et al 2007 [106] | Relapsed /refractory GCT | Phase II trial | 41 | Gemcitabine, Oxaliplatin and Paclitaxel | CR 5%  (15% CR to chemo + surgery0 | 3.0 | 6 | 78% had relapsed after HDCT and stem cells.  73% relapsed <3m after platinum |
| Kollmannsberger et al 2004 [107] | Relapsed /refractory GCT | Phase II trial | 35 | Gemcitabine and Oxaliplatin | ORR 46%  CR 9% | 11% at 6 months follow-up | 6 | 89% had prior HDCT + stem cells  63% platinum refractory |
| Einhorn et al 2007[108] | Relapsed /refractory GCT | Retrospective review | 32 | Paclitaxel and Gemcitabine | ORR 31%  CR 19% | Not available | 8 | All patients had progressed after HDCT + stem cells |
| Hinton et al 2002 [109] | Relapsed /refractory GCT | Phase II trial | 28 | Paclitaxel and Gemcitabine | ORR 21.4%  CR 11% | Not available | 8.3 | 75% had ≥2 prior platinum regimens.  36% cisplatin refractory.  36% had prior HDCT. |

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