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# In vitro phase II comparison of the cytotoxicity of a novel platinum analog, nedaplatin (254-S), with that of cisplatin and carboplatin against fresh, human ovarian cancers

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**Abstract** *Purpose*: To compare the in vitro cytotoxicity of nedaplatin, an investigational platinum analog, with that of the standard platinum agents, cisplatin and carboplatin, against fresh human, epithelial ovarian cancers. *Methods*: The Hamburger-Salmon human tumor colony-forming assay (HTCA) was used to measure the chemosensitivity of 36 fresh tumor samples obtained during initial exploratory laparotomy from patients with newly diagnosed stage III–IV epithelial ovarian cancer who had received no prior chemotherapy or radiation therapy. Tumor samples were exposed to the platinum analogs for 1 h at concentrations of 10 and 100 μg/ml of nedaplatin and cisplatin and 100 and 1000 μg/ml of carboplatin. The resulting survival data were used to estimate the $IC_{50}$ (drug concentration associated with 50% inhibition of tumor colony forming units, TCFUs) of each of the platinum analogs for each of the tumor samples, as well as the estimated survival following exposure to clinically achievable drug levels (i.e. the ultrafiltrable platinum area under the plasma disappearance curve, AUC, achieved in cancer patients following administration of standard or phase II doses). *Results*: At the lowest concentration tested (i.e. 10 μg/ml nedaplatin and cisplatin and 100 μg/ml carboplatin) the percentages of tumor samples which were sensitive (as defined by 50% or less survival of TCFUs as compared with controls) were 42, 50, and 40% for nedaplatin, cisplatin and carboplatin, respectively. The median $IC_{50}$ values were 28.5, 12 and 121 μg/ml for nedaplatin, cisplatin and carboplatin, respectively. The estimated percentage of tumors sensitive to clinically achievable dose levels was 42% for nedaplatin and 36% for cisplatin and carboplatin. Nedaplatin and carboplatin proved relatively crossresistant with cisplatin in vitro; of the 18 tumor samples which were resistant to cisplatin, only 5 (28%) were sensitive to nedaplatin and 3 of 17 (18%) were sensitive to carboplatin. *Conclusion*: Nedaplatin was associated with cytotoxicity similar to cisplatin and carboplatin in this study. Although nedaplatin appears to be crossresistant with cisplatin, its high rate of in vitro cytotoxicity, relative lack of neurotoxicity and nephrotoxicity, and large in vivo bioavailability establish nedaplatin as a promising platinum analog for further clinical development as a salvage and primary chemotherapeutic agent for patients with advanced ovarian cancer.

**Key words** Platinum analog · Nedaplatin · Chemotherapy · Ovarian cancer

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## Introduction

The platinum compounds, cisplatin and its analog carboplatin, are important chemotherapeutic agents used in the initial treatment of ovarian and other solid cancers [10, 13, 15, 16]. Unfortunately, most patients who initially achieve a complete response to platinum-based therapy develop resistance to these drugs [13, 15]. Additionally, many patients who are treated with cisplatin develop dose-limiting neurotoxicity, hearing loss, and nephrotoxicity [3, 8]. Although carboplatin is more myelosuppressive than the parent agent, cisplatin, it is associated with significantly less renal, neurological and ototoxicity; however, it demonstrates almost complete crossresistance to cisplatin [4, 12]. Thus, research is ongoing to further reduce toxicities, and circumvent resistance to standard platinum agents (e.g. through the use of chemomodulating agents), and also to develop noncrossresistant analogs.

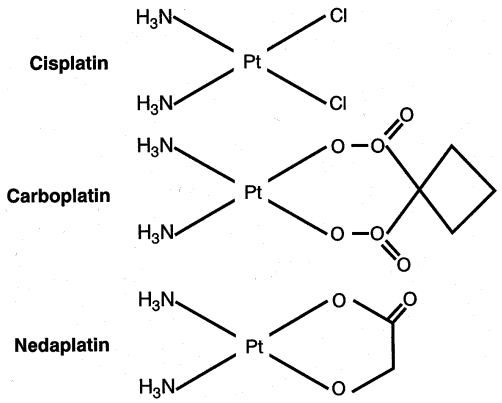


**Fig. 1** Chemical structures of cisplatin, carboplatin and nedaplatin

Nedaplatin is an experimental platinum analog which has undergone recent clinical evaluation. It was selected from a series of platinum analogs for clinical evaluation based on its pronounced preclinical antitumor activity against solid tumors, virtual lack of nephrotoxicity and relatively low rate of neurotoxicity [20–22]. Results of phase I and phase II studies have revealed a spectrum of solid tumor activity similar to that of cisplatin [2, 5, 9, 14, 18, 19]. Its dose-limiting toxicity appears to be myelosuppression, particularly thrombocytopenia. Nedaplatin also has been associated with ototoxicity similar to that observed with cisplatin [2, 5].

The chemical structures of nedaplatin, cisplatin and carboplatin are displayed in Fig. 1. All three agents undergo hydrolysis, although at different rates, to form active divalent species which ultimately form DNA intrastrand adducts.

In this study, we performed a comparative examination of the in vitro activity of nedaplatin, cisplatin and carboplatin against fresh human ovarian tumor samples using the Hamburger-Salmon human tumor colony-forming assay (HTCA) [7, 11, 17].

## Materials and methods

### Tumor samples

Solid tumor biopsy specimens were obtained from 36 previously untreated patients with epithelial, ovarian cancer (FIGO stage III-IV) during the initial exploratory laparotomy and tumor debulking surgery. Specimens were transferred aseptically to our HTCA laboratory within 24 h of surgery. Solid tumor specimens were transported in medium (McCoys 5A, Irvine, Santa Ana, Calif.) supplemented with 10% fetal bovine serum (FBS), penicillin (100 units/ml), streptomycin (100 mg/ml) and L-glutamine (2 m*M*) (Irvine).

### Drug preparation

Tumor specimens underwent drug sensitivity testing with multiple standard and investigational agents. Cisplatin (clinical sample, Bristol-Myers Squibb Oncology, Princeton, N.J.) was reconstituted in distilled water to give 1 mg/ml cisplatin in 10 mg/ml mannitol. Further dilutions were made with 0.9% NaCl. Carboplatin (clinical sample, Bristol-Myers Squibb Oncology) and nedaplatin (research sample, Shionogi and Company Ltd., Osaka, Japan) were reconstituted in distilled water.

### HTCA method

The HTCA was performed with minor modification as previously described for epithelial cancers of the ovary [7, 11, 17]. Solid tumor samples were minced into 2–3-mm pieces and then further digested in 8 ml 0.15% type I collagenase, 0.015% DNase mixture (Sigma, St. Louis, Mo.) and 8 ml hypo-osmotic medium in a stirring flask for 1.0 h at 37 °C. The digest was then filtered through 8X sterile gauze and washed with McCoy's 5A medium supplemented with 10% FBS. The resulting cell suspension was examined and, if necessary, a 25- or 30-μm mesh filtration was used to obtain a single-cell suspension.

Drug incubations were performed in triplicate at 37 °C for 1 h in McCoy's 5A medium supplemented with 10% FBS. Standard drug exposures were 0, 10, and 100 μg/ml for nedaplatin and cisplatin and 0, 100, and 1000 μg/ml for carboplatin.

After drug incubation, the tumor cells were washed twice with 5 ml McCoy's 5A medium supplemented with 10% FBS and plated as previously described [11, 17] Tumor cells were plated at a concentration of approximately 250 000 cells/plate. Plates were incubated for 14 to 21 days at 37 °C in an atmosphere containing 5% $CO_2$, stained with INT stain (Pfaltz and Bauer, Stamford, Ct.) and colonies were counted on an Omnicon Image Analyzer [17]. The plant lectin, abrin (Sigma, St. Louis, Mo.), was used as a positive control in each experiment.

### Estimation of percent tumor colony-forming unit (TCFU) survival at clinically achievable drug concentrations

The minimum platinum drug doses used in this study (10–100 μg/ml for 1 h) were rough approximations of clinically achievable drug concentrations as defined by the mean ultrafiltrable platinum plasma AUC following administration of standard doses for single agent chemotherapy of gynecologic cancers (16 μg×h/ml for nedaplatin, 9.8 μg×h/ml for cisplatin, and 80 μg×h/ml for carboplatin) [6, 18, 23]. We refined our estimation of clinical activity further by predicting the percentage survival relative to control of individual tumor samples at a dose equal to the mean ultrafiltrable platinum plasma AUC using a least squares fitted model with log(dose +1) as the predictor.

## Results

### Ovarian tumor samples

A total of 36 viable tumor samples from chemotherapy-naive patients with epithelial ovarian cancer with stage III and IV were tested against each of the three platinum analogs, using the HTCA.

### In vitro drug sensitivity data

Shown in Table 1 are the in vitro chemosensitivity data (expressed as percent survival of TCFU growth as compared with control plates) for each of the 36 different fresh ovarian cancers exposed separately to each of the three platinum-containing analogs for 1 h. All three agents exhibited strong dose-response relationships against the majority of the 36 cancers. With chemosensitivity being defined as ≤50% survival of TCFUs as compared with control plates, 15 of 36 cancers (42%) were sensitive to

**Table 1** Percent survival of TCFUs obtained from fresh human ovarian cancers following a 1-h exposure to three platinum analogs at the specified in vitro concentrations (*NA* data not available)

| Tumor sample number | Nedaplatin 10 μg/ml | Cisplatin 10 μg/ml | Carboplatin 100 μg/ml |
|---|---|---|---|
| 8332 | 131 | 99 | 111 |
| 8324 | 14 | 33 | 26 |
| 8320 | 84 | 86 | 96 |
| 8318 | 35 | 29 | 15 |
| 8316 | 50 | 43 | 41 |
| 8305 | 84 | 50 | 50 |
| 8302 | 51 | 60 | 54 |
| 8299 | 47 | 37 | 79 |
| 8297 | 54 | 68 | 61 |
| 8295 | 68 | 34 | 65 |
| 8287 | 22 | 9 | 15 |
| 8285 | 91 | 84 | 102 |
| 8260 | 95 | 87 | 82 |
| 8256 | 18 | 36 | 38 |
| 8249 | 94 | 55 | 138 |
| 8246 | 72 | 73 | 43 |
| 8228 | 28 | 21 | 18 |
| 8206 | 94 | 23 | 42 |
| 8204 | 45 | 58 | 85 |
| 8202 | 29 | 41 | 39 |
| 8198 | 39 | 30 | 96 |
| 8192 | 90 | 44 | 62 |
| 8183 | 46 | 74 | 75 |
| 8180 | 46 | 62 | 81 |
| 8178 | 64 | 29 | 53 |
| 8170 | 45 | 76 | 45 |
| 8165 | 76 | 51 | 70 |
| 8163 | 46 | 97 | 50 |
| 8154 | 98 | 71 | NA |
| 8148 | 72 | 37 | 54 |
| 8146 | 106 | 52 | 83 |
| 8140 | 92 | 62 | 67 |
| 8132 | 81 | 82 | 60 |
| 8127 | 60 | 26 | 73 |
| 8120 | 19 | 8 | 45 |
| 8118 | 58 | 41 | 38 |
| Number tumors tested | 36 | 36 | 35 |
| Median % survival | 59 | 50.5 | 60 |
| Number sensitive (%)[a] | 15/36 (42) | 18/36 (50) | 14/35 (40) |

[a] Sensitivity is defined as ≤50% survival of TCFUs relative to control plates

**Table 2** $IC_{50}$ values (drug concentration associated with 50% inhibition of TCFUs relative to control) of platinum-containing analogs against 36 fresh human ovarian tumors (*UNACH* unachievable)

| Tumor sample numer | Nedaplatin (μg/ml) | Cisplatin (μg/ml) | Carboplatin (μg/ml) |
|---|---|---|---|
| 8332 | UNACH | 61 | UNACH |
| 8324 | 5 | 10 | 49 |
| 8320 | UNACH | 45 | UNACH |
| 8318 | 6 | 8 | 25 |
| 8316 | 29 | 11 | 97 |
| 8305 | 72 | 20 | 100 |
| 8302 | 12 | 13 | 68 |
| 8299 | 14 | 14 | 1225 |
| 8297 | 25 | 21 | 915 |
| 8295 | 51 | 12 | 101 |
| 8287 | 5 | 6 | 23 |
| 8285 | UNACH | 53 | UNACH |
| 8260 | 103 | 107 | 298 |
| 8256 | 6 | 9 | 47 |
| 8249 | 77 | 12 | UNACH |
| 8246 | 50 | UNACH | 130 |
| 8228 | 14 | 8 | 32 |
| 8206 | 85 | 7 | 42 |
| 8204 | 35 | 16 | 290 |
| 8202 | 5 | 9 | 39 |
| 8198 | 9 | 7 | 307 |
| 8192 | 72 | 10 | 118 |
| 8183 | 29 | 100 | UNACH |
| 8180 | 11 | 12 | 167 |
| 8178 | 12 | 7 | 50 |
| 8170 | 8 | 19 | 59 |
| 8165 | 28 | 10 | 124 |
| 8163 | 33 | 110 | 177 |
| 8154 | UNACH | UNACH | UNACH |
| 8148 | 28 | 9 | 62 |
| 8146 | 52 | 10 | 357 |
| 8140 | 112 | 23 | 556 |
| 8132 | UNACH | UNACH | UNACH |
| 8127 | 11 | 7 | 98 |
| 8120 | 4 | 5 | 39 |
| 8118 | 16 | 6 | 42 |
| Number achievable/number tested | 31/36 | 33/36 | 29/36 |
| Median $IC_{50}$ of all values | 28.5 | 12 | 121 |
| Mean of achievable values ± standard error | 33±6 | 24±5 | 194±51 |

nedaplatin at a concentration of 10 μg/ml, 18 of 36 (50%) to cisplatin at 10 μg/ml and 14 of 35 (40%) to carboplatin at 100 μg/ml. The 100 μg/ml concentration of carboplatin is roughly comparable to the 10 μg/ml cisplatin concentration, based on carboplatin's larger clinically achievable AUC, slow in vitro activation rate, and prior in vitro HTCA training set analysis against human tumor cell lines. The chemosensitivity rates for the three drugs were not significantly different from one another.

The concentrations of each platinum analog associated with 50% survival of TCFUs (i.e. $IC_{50}$ values) are listed in Table 2. The median $IC_{50}$ values for nedaplatin, cisplatin and carboplatin were 28.5, 12 and 121 μg/ml, respectively. The corresponding mean (±standard error) $IC_{50}$ values were 33±6, 24±5, and 194±51 μg/ml, respectively. There were no statistically significant differences between the $IC_{50}$ values of cisplatin and nedaplatin ($P > 0.1$, McNemar's test). Carboplatin's $IC_{50}$ values were artifactually high owing to its slow in vitro activation.

Based on the raw percent TCFU survival data presented in Table 1, we evaluated the cross-sensitivity and cross-resistance of carboplatin and nedaplatin, relative to the activity of cisplatin. As shown in Table 3, of the 18 ovarian cancers sensitive to cisplatin (i.e. ≤50% survival of TCFUs), 10 (56%) also were sensitive to nedaplatin and 11 (61%) to carboplatin. Of the 18 cancers resistant to cisplatin (i.e. >50% survival of TCFUs), only 5 of 18 (28%) and 3 of 17 (18%) were sensitive to nedaplatin and carboplatin, respectively.

Human pharmacokinetic studies have shown that following the administration of clinically tolerable and biologically active doses of nedaplatin, cisplatin and carboplatin (i.e. 100, 100 and 400 mg/m$^2$, respectively), mean plasma ultrafiltrable platinum AUCs are 16, 9.8 and 80 μg×h/ml,

**Table 3** Chemosensitivity (defined as ≤50% of TCFUs relative to control at doses of 10 μg/ml for cisplatin and nedaplatin and 100 μg/ml for carboplatin) of fresh ovarian tumors to nedaplatin and carboplatin, relative to cisplatin

| | Sensitive to nedaplatin 15/36 (42%) | Sensitive to carboplatin 14/35 (40%) |
|---|---|---|
| Sensitive to cisplatin 18/35 (50%) | 10/18 (56%) | 11/18 (61%) |
| Resistant to cisplatin 18/36 (50%) | 5/18 (28%) | 3/17 (18%) |

respectively [6, 18, 23]. The estimated percent TCFU survivals of all the ovarian cancers included in this study at the clinically achievable plasma levels (i.e. mean plasma AUCs) of the three platinum analogs are shown in Table 4. Based on these calculations, the activities of nedaplatin, cisplatin and carboplatin were roughly comparable with 42% of tumors sensitive to nedaplatin and 36% sensitive to cisplatin and carboplatin at clinically achievable concentrations.

## Discussion

The platinum compounds, cisplatin and carboplatin, continue as two of the most commonly used anticancer drugs in the treatment of a variety of solid tumors, including cervix, head and neck, lung and ovarian cancers [15]. Unfortunately, both inherent and acquired tumor resistance to these drugs limit their clinical utility [13]. Thus, there has been a continued search for more active and noncrossresistant platinum analogs. Nedaplatin is one such drug which has undergone clinical testing in Japan.

We compared the in vitro cytotoxicities of nedaplatin, cisplatin and carboplatin against 36 fresh ovarian cancers from chemotherapy-naive patients using the HTCA. Nedaplatin, cisplatin and carboplatin were tested at 10 and 100 μg/ml dose levels and carboplatin was tested at 100 and 1000 μg/ml. At the lowest drug concentration tested (i.e. 10 μg/ml for nedaplatin and cisplatin and 100 μg/ml for carboplatin) the percentage of tumor samples which were sensitive (as defined by 50% or less survival of TCFUs as compared with controls) was 42%, 50% and 40% for nedaplatin, cisplatin and carboplatin, respectively.

We have established previously that the clinical relevance of in vitro data may be increased by consideration of human pharmacokinetic data, especially the mean plasma concentration time product (AUC) during the dose selection process [1]. Human pharmacokinetic studies have shown that following the administration of clinically tolerable and biologically active doses of nedaplatin, cisplatin and carboplatin (i.e. 100, 100 and 400 mg/m$^2$, respectively), mean plasma ultrafiltrable platinum AUCs are 9.8, 16 and 80 μg×h/ml, respectively [6, 18, 23]. The minimum platinum drug doses used in this study were within the region of clinically achievable levels. We refined the estimation of clinical activity further by using a least squares fitted linear model to estimate the percent survival of TCFUs at the mean plasma AUCs listed above for the three platinum agents. The estimated percentage of sensitive tumors at the clinically achievable AUC was 42% for nedaplatin and 36% for cisplatin and carboplatin. Thus, nedaplatin appears to have comparable activity to cisplatin and carboplatin on the basis of the degree of sensitivity at the minimum dose tested, as well as at the clinically achievable AUC.

We showed that nedaplatin, as well as carboplatin, appear relatively crossresistant with cisplatin in vitro. For example, only 28% of the ovarian cancers resistant to cisplatin were sensitive to nedaplatin and only 18% were sensitive to carboplatin. Other studies have shown a partial crossresistance of nedaplatin to other platinum agents [2, 9]. Thus, nedaplatin, like carboplatin, may not prove useful as

**Table 4** Estimated percent survival of TCFUs at clinically achievable drug levels (i.e. mean free platinum plasma AUC following administration of standard doses[a])

| Tumor sample number | Nedaplatin | Cisplatin | Carboplatin |
|---|---|---|---|
| 8332 | 105 | 73 | 113 |
| 8324 | 31 | 50 | 44 |
| 8320 | 107 | 69 | 104 |
| 8318 | 33 | 46 | 33 |
| 8316 | 59 | 52 | 52 |
| 8305 | 68 | 61 | 53 |
| 8302 | 45 | 55 | 48 |
| 8299 | 47 | 55 | 70 |
| 8297 | 57 | 62 | 68 |
| 8295 | 65 | 53 | 53 |
| 8287 | 29 | 39 | 31 |
| 8285 | 73 | 71 | 82 |
| 8260 | 73 | 76 | 63 |
| 8256 | 31 | 48 | 43 |
| 8249 | 68 | 53 | 88 |
| 8246 | 64 | 78 | 55 |
| 8228 | 48 | 45 | 37 |
| 8206 | 69 | 42 | 42 |
| 8204 | 58 | 58 | 62 |
| 8202 | 32 | 47 | 41 |
| 8198 | 39 | 45 | 62 |
| 8192 | 67 | 51 | 54 |
| 8183 | 58 | 74 | 74 |
| 8180 | 43 | 53 | 58 |
| 8178 | 45 | 44 | 44 |
| 8170 | 40 | 61 | 46 |
| 8165 | 59 | 51 | 55 |
| 8163 | 60 | 78 | 57 |
| 8154 | 94 | 79 | 85 |
| 8148 | 58 | 49 | 47 |
| 8146 | 66 | 51 | 63 |
| 8140 | 71 | 62 | 65 |
| 8132 | 95 | 90 | 72 |
| 8127 | 43 | 43 | 53 |
| 8120 | 25 | 37 | 40 |
| 8118 | 50 | 42 | 42 |
| Median % survival | 58 | 53 | 55 |
| Number sensitive (%)[b] | 15/36 (42) | 13/36 (36) | 13/36 (36) |

[a] Mean free platinum AUCs were 16 μg×h/ml following a nedaplatin dose of 100 mg/m$^2$, 9.8 μg×h/ml following a cisplatin dose of 100 mg/m$^2$, and 80 μg×h/ml following a carboplatin dose of 400 mg/m$^2$

[b] Sensitivity defined as ≤50% survival of TCFUs compared to control

a salvage agent in patients with cisplatin-refractory (or carboplatin-refractory) tumors; however, because of its relative lack of associated neurotoxicity and nephrotoxicity and high bioavailability, nedaplatin merits further clinical trials in both previously untreated and treated patients with advanced ovarian cancers.

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