Efficacy with a Replication-selective Adenovirus Plus Cisplatin-based Chemotherapy: Dependence on Sequencing but not p53 Functional Status or Route of Administration

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ABSTRACT

Replication-selective adenoviruses are being developed as novel anticancer therapeutics. Clinical trials with dl 1520, an E1B-M, 55,000 gene-deleted adenovirus (ONYX-015), have demonstrated selective viral replication and biological activity in head and neck and ovarian carcinomas, but durable objective responses were not demonstrated. However, clinical results suggested potentially synergistic interactions with platinum-containing chemotherapy. To better characterize and optimize this interaction, we carried out combined modality treatment with ONYX-015 and cisplatin-based chemotherapy in three nude mouse-human tumor xenograft models with differing tumor locations or p53 functional status. Superior efficacy was demonstrated with combination therapy over either agent alone in all three models, independent of the route of ONYX-015 administration (intratumoral or i.p.). Virus replication was not demonstrably inhibited by cisplatin plus 5-fluorouracil chemotherapy. To assess the role of p53 function or cisplatin resistance in this interaction, we treated ovarian carcinomas that were matched except for p53 functional status (A2780, A2780/CP70). Combination therapy led to improved survival over either agent alone in both the p53(−) and the p53(+) carcinomatosis models. Efficacy was highly dependent on the sequencing of the agents; treatment with ONYX-015 prior to, or simultaneously with, chemotherapy was significantly superior to chemotherapy followed by ONYX-015. These results support further evaluation of replication-selective adenoviruses and cisplatin-based chemotherapy in clinical trials.

INTRODUCTION

Localized squamous cell carcinomas of the head and neck region can be treated with surgery, radiotherapy, radiotherapy plus surgery, or radiotherapy plus chemotherapy. However, locoregional recurrence occurs frequently (1). Once these tumors recur, they are almost uniformly fatal. Once surgery and radiotherapy have failed, the standard chemotherapy regimen used is cisplatin plus 5-FU (2). Objective responses are induced in only 35% of patients with recurrent disease (3–5), in general, and response durations are typically short (6). Patients with ovarian carcinomas also suffer from regional relapse after primary surgery and platinum-based chemotherapy (7, 8); these relapses occur within the peritoneal cavity. Therefore, these patients need novel locoregional therapies that are effective in combination with platinum-based chemotherapy.

Replication-selective adenoviruses are being developed as cancer therapies. ONYX-015 (dl 1520) is an E1B-M, 55,000 gene-deleted adenovirus (9) that replicates in and lyases tumor cells with defects in the p53 pathway (10–13). ONYX-015 is in clinical trials in patients with head and neck cancer or ovarian cancer, the majority of which are deficient in p53 function. The p53 pathway is frequently altered in these tumors through p53 gene mutations (1, 14–20), mdm-2 overexpression (21), or human papillomavirus E6 protein expression (22). In addition, development of cisplatin resistance can itself be associated with apparent loss of p53 function without gene mutation (23, 24). Additionally, recurrent head and neck cancers are amenable to direct i.t. injection without radiographic guidance (25), and i.p. treatments are frequently administered to ovarian cancer patients. Finally, most morbidity and even mortality in these diseases occurs as a result of locoregional progression (3). Therefore, locoregional therapy for these diseases can potentially lead to enhanced quality of life and even improved survival.

ONYX-015 has been well tolerated in Phase I and II trials. Patients with recurrent and refractory head and neck cancer have received i.t. injections for up to 5 consecutive days repeated every 3 weeks (25, 26), whereas ovarian cancer patients received i.p. administrations on a similar schedule.4 Although selective replication within tumor cells and biological activity were demonstrated, durable objective responses were not achieved in these patients. However, durable regressions were subsequently achieved in combination with cisplatin-based chemotherapy in head and neck cancer patients (27). Importantly, ONYX-015 and cisplatin do not have overlapping toxicities (11). Given the radically different mechanisms of action of viral and chemotherapeutic agents, cross-resistance is theoretically unlikely. To define optimal sequencing regimens and

3 The abbreviations used are: 5-FU, 5-fluorouracil; i.t., intratumoral; pfu, plaque-forming units; TNF, tumor necrosis factor.
4 S. Kaye, personal communication.
evaluate effects of chemotherapy on virus replication, we carried out nude mouse-human tumor xenograft studies of single-agent versus combined modality therapy with ONYX-015 and cisplatin-based chemotherapy in both head and neck and ovarian cancer xenografts. Different tumor histologies (head and neck squamous versus ovarian carcinomas) and routes of ONYX-015 administration (i.t., i.p.) were evaluated. To assess the role of p53 functional status in this interaction, we treated ovarian carcinomas that were matched except for these variables (A2780, A2780/CP70). Combination therapy led to improved survival over either agent alone in all three models. This efficacy was highly dependent on the sequencing of the agents but independent of p53 functional status.

MATERIALS AND METHODS

Viruses

ONYX-015 (dl1520) is a chimeric human group C adenovirus (Ad2 and Ad5) that does not express the $M_{r}$ 55,000 product of the E1B gene (9). The virus contains a deletion between nucleotides 2496 and 3323 in the E1B region encoding the $M_{r}$ 55,000 protein. In addition, a C→T transition at position 2022 in E1B generates a stop codon at the third codon position of the protein. Wild-type D adenovirus is identical to ONYX-015 except in E1B, where the original, wild-type sequence is present. All adenoviruses were grown on the human embryonic kidney cell line HEK293 as described previously (10). The negative control virus was prepared by UV inactivating a duplicate sample of ONYX-015 prepared on the day of injection. UV inactivation was achieved by exposing the virus sample to three consecutive cycles of 120,000 mJoules in a UV Stratalinker.

Cell Lines

HLA-c human squamous cell carcinoma cells of the larynx were obtained from Dr. Dan Von Hoff (Cancer Therapy and Research Center, San Antonio, TX). HLaC cells have a normal p53 gene sequence but lack the p53-mediated G1-S phase cell cycle arrest response to $\gamma$-irradiation (11). A2780 ovarian carcinoma has a normal p53 gene sequence and a normal G1 arrest response after $\gamma$-irradiation (28). The A2780/CP70 subclone was selected through serial passage in the presence of cisplatin and is consequently highly resistant to cisplatin, whereas the A2780/Ad line is relatively resistant to doxorubicin. Although the p53 gene sequence is reportedly normal, the p53-mediated G1 arrest response to $\gamma$-irradiation is abnormal, evidence for at least a partial loss of p53 function (23).

Animals and Animal Care

Female athymic nu/nu mice were obtained from Harlan Sprague Dawley Co. at 4–6 weeks of age and quarantined for 2 weeks prior to being eligible for entry into the study. During and after the quarantine period, mice were housed four/cage in Allentown M1 cages fitted with micro-isolator tops and allowed access to Purina rodent chow 5001 and tap water ad libitum. Federal guidelines for animal care were strictly followed.

Nude Mouse-Human Tumor Xenograft Efficacy Studies

HLA-C Human Laryngeal Carcinoma. Tumor cells (2 × 10$^{6}$ cells) were injected into the flanks of athymic nude mice, 6–8 weeks of age, and allowed to grow into palpable tumors of ~100 mm$^3$ (5–8 mm, maximal diameter). Tumors were injected with either 10$^{6}$ pfu of ONYX-015 or UV-inactivated control virus suspended in 60 µl of carrier (PBS) daily for 5 days; daily injections were distributed equally into each of four tumor quadrants. For the combined virus plus chemotherapy treatment groups, the standard clinical regimen of cisplatin and 5-FU was used. i.p. administrations of 5-FU (30 mg/kg/day) and cisplatin (3 mg/kg/day) were given for 5 consecutive days. Mice (9–10/group) received either ONYX-015 alone (plus i.p. saline), chemotherapy alone (plus i.t. vehicle), ONYX-015 and chemotherapy (simultaneously on days 1–5), or neither (vehicle injection into the tumor and saline injections into the peritoneum). To address treatment sequencing, additional groups of 10 mice each were treated with ONYX-015 and chemotherapy in identical fashion as above, except for the duration of the therapies. One group received ONYX-015 on days 1–5 and chemotherapy on days 8–12, whereas the other group received the two treatments in the reverse order. Tumor measurements were taken weekly, and the animals were sacrificed once their tumors grew to >1 cm$^3$. Tumor responses to treatment were defined as follows (within 2 weeks after treatment initiation): complete response (no evidence of residual tumor); partial response (50–99% reduction in volume); stable disease (+ or −, 0–25%); and progressive disease (>25% increase).

A2780 and A2780/Cp70 Ovarian Carcinoma Model. Cells (10$^5$) were suspended in 0.5 ml of PBS and injected into the peritoneal cavity of female athymic nu/nu mice and passaged in vivo once before being used in treatment protocols. The effect of treatment on survival was evaluated using the A2780 p53+ parental cell line. ONYX-015 (1 × 10$^6$ pfu/day on study days 1–5) was administered either before or simultaneously with cisplatin. Cisplatin was dosed at 4 mg/kg every other day for 3 days (total dose, 12 mg/kg), i.e., study days 1, 3, 5 or days 8, 10, 12. All treatments were administered i.p., and there were 12 mice/treatment group. The mean A2780 tumor burden of 13 mice at study initiation was 0.59 ± 1.2 g. The effect of treatment on tumor burden was evaluated in nude mice bearing A2780/CP70 ovarian tumors (in vitro cisplatin-resistant ovarian tumor cell line). ONYX-015 was administered before, after, or simultaneously with cisplatin with identical doses as the A2780 survival study described above. Mean tumor burden at study initiation for 8 mice was 0.93 ± 1.4 g. Animals were scheduled for euthanasia 3 weeks after initiation of treatment; however, mice that were moribund were sacrificed earlier. At necropsy, tumors were removed and weighed. There were eight mice/treatment group and six untreated controls.

In Vivo Effects of Chemotherapy on Viral Replication. Ten HLaC tumor-bearing mice were treated with either ONYX-015 alone (n = 5) or simultaneous ONYX-015 with cisplatin and 5-FU on study days 1–5 (n = 5). On day 8 after treatment initiation, the animals were sacrificed, and the tumors were excised. Half was flash frozen in liquid nitrogen for virus titration, and the other half was formalin fixed and processed for histopathology and in situ hybridization. For virus titration, specimens were minced with sterile scalpels, and tissue was further dissociated through a mesh screen. Virus was extracted from the homogenate by three consecutive freeze/thaw cycles and centrifuged, and the supernatant was used to determine the
RESULTS

Antitumoral Efficacy of ONYX-015 and Chemotherapy Is Superior to Each as a Single Agent by Both Intratumoral and i.p. Administration. Beneficial effects were seen after combination treatment with virus plus chemotherapy in both the s.c. laryngeal tumor xenografts and in a model of ovarian carcinomatosis. The chemotherapy agents used are those used clinically for head and neck cancer (cisplatin and 5-FU) and ovarian carcinoma (cisplatin). Nude mice with s.c. HLaC laryngeal human tumor xenografts were treated with either ONYX-015 by direct i.t. injection, with i.p. injections of cisplatin and 5-fluorouracil, or both modalities (n = five treatment groups plus one PBS control). Animals treated with both modalities received them concurrently or sequentially (virus followed by chemotherapy or the reverse). Although all treatment groups had superior survival to the PBS control group (Fig. 1B), the improvement was statistically significant for only two treatment groups (Table 1): ONYX-015 followed by chemotherapy (P = 0.03) and concurrent ONYX-015 and chemotherapy (P = 0.05). These two treatment groups also had the greatest tumor growth inhibition (Fig. 1A) and the highest complete response rates, 33 and 20%, respectively, versus 10% for ONYX-015 alone and 0% for chemotherapy alone. No increase in toxicity was seen with combination therapy versus PBS; animal weights, behavior, and appearance were similar in all groups.

The effects of single-agent and combination therapy on tumor growth and survival were also assessed in the A2780/CP70 peritoneal carcinomatosis model (Table 2). Because tumor measurement over time was not possible in the ovarian i.p. model, we assessed overall survival (log-rank analysis) and the presence or absence of tumors on day 30. Survival on day 30 was superior for the combination therapy group (100%) versus either monotherapy group (75%) or PBS controls (17%; P = 0.02 for combination therapy versus PBS; log-rank test). On day 30, animals treated with ONYX-015 followed by cisplatin were tumor free in 38% of cases versus 12% with ONYX-015 alone, 0% with chemotherapy alone, and 0% with PBS (P = 0.05 for combination therapy versus either single-agent alone or PBS).

Antitumoral Efficacy of Single-Agent versus Combination Therapy in a p53-functional Tumor. To determine whether functional p53 could block combination therapy efficacy, we tested the combination in the parental A2780 carcinoma line. In contrast to A2780/CP70 cells, A2780 tumor cells have intact p53 induction and G1-S arrest in response to chemotherapy (have an intact p53-mediated arrest function). In the A2780 ovarian carcinomatosis model, cisplatin or ONYX-015 treatments alone had no effect on survival, but ONYX-015 followed by cisplatin did (Fig. 2; P = 0.06 versus monotherapy groups or PBS; log-rank test). Survival on day 70 was superior for the combination therapy group (70%) versus either monotherapy group (18%) or PBS controls (21%; P = 0.02 for combination therapy versus PBS; log-rank test). Therefore, combination therapy was superior to single-agent therapy, even in a model with intact p53 function.

Relative Efficacy of Combination Therapy Regimens. The relative efficacy of three different combination therapy sequences were compared: virus before chemotherapy, chemotherapy before virus, and concurrent treatment. Virus before chemotherapy was the most effective regimen in both the s.c. and the i.p. models. In the s.c. HLaC model, virus before chemotherapy and concurrent therapy both resulted in significantly prolonged survival versus chemotherapy before virus (P = 0.02 and 0.04, respectively; Table 1; Fig. 3A). Complete responses
were also more common in these groups: 33% and 20% versus none, respectively (Table 1). On day 15, tumor volumes were 212 ± 62 mm³ (P = 0.006 versus PBS), 260 ± 55 mm³ (P = 0.01 versus PBS), and 547 ± 143 mm³ (P = 0.39 versus PBS), respectively. Day 22 mean tumor volumes were 238 ± 76 mm³ with virus before chemotherapy and 405 ± 115 mm³ with concurrent therapy (measurements for the third group were censored because of animal deaths by day 22; Fig. 3B).

To determine the generalizability of this finding, we compared the same regimens in an i.p. ovarian tumor model with a different tumor type and with a different route of administration (i.p. virus). Similar results were seen in the ovarian carcinomatosis model, as outlined in Table 2. Survival of animals treated with ONYX-015 followed by chemotherapy was superior to those treated with chemotherapy followed by ONYX-015 (P = 0.08); the fraction of animals that were tumor free on day 30 was also greater with ONYX-015 followed by chemotherapy (P = 0.07).

**In Vivo Effects of Chemotherapy on Viral Replication.**
No effect of chemotherapy on viral replication was demonstrable by either virus titration or in situ hybridization. Viral titers on day 8 were identical after treatment with ONYX-015 alone (7.43 × 10⁹) or in combination with concurrent cisplatin and 5-FU (10.2 × 10⁹; Fig. 4A). In situ hybridization demonstrated equivalent disseminated intratumoral viral replication in both groups (Fig. 4B). We have previously used in situ hybridization to assess viral replication within the A2780 tumor cells +/− p53 function growing i.p. (Heise et al., Gene Therapy, in press). We demonstrated positive, low level replication in the p53(−) A2780 tumor cells but not in the p53(+) cells.

**DISCUSSION**
These results demonstrate that combining ONYX-015 with cisplatin-based chemotherapy leads to increased efficacy over that seen with either modality alone in models of: (a) i.t. or i.p. administration of ONYX-015; (b) p53-deficient or p53-functional tumors; and (c) different tumor histologies. Treatment with the virus followed by cisplatin-based chemotherapy, or concurrent therapy, were superior to treatment with cisplatin followed by virus in these two models. No significant inhibition of viral replication by chemotherapy was demonstrated. Finally, no demonstrable increase in toxicity was seen. It therefore does not appear that ONYX-015 enhanced the toxicity of chemotherapy. ONYX-015 oncolytic adenoviral therapy was combined with cisplatin-based chemotherapy for several reasons: (a) antitumoral activity had been documented for each agent independently in these tumors; and (b) overlapping toxicities had not been demonstrated; we therefore predicted that these agents could be safely combined without a significant increase in toxicity over either agent alone. For example, none of the myelosuppression, renal toxicity, or peripheral neuropathies associated with cisplatin had been documented with ONYX-015 alone. Finally, cross-resistance between a viral therapy and chemotherapy was unlikely, given the divergent mechanisms of action. Although previous mouse tumor model studies had documented the feasibility of combining replication-selective adenoviruses with chemotherapy (11, 13, 30), no sequence optimization had been performed, only s.c. and p53-deficient tumors had been tested, and the impact of chemotherapy on viral replication was not studied. We therefore believe that these results represent a significant advance for this therapeutic platform.

Further studies will be performed to determine the specific mechanism(s) involved in this interaction. These studies cannot delineate between additive or synergistic effects of combining these two treatment modalities in the models described; formal testing for synergy has not been carried out in vivo. Clinical data, and some preclinical models, have suggested a synergistic

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**Table 1** Comparison of survival and complete response rates between treatment groups in the s.c. HLaC tumor model

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Median survival (days)</th>
<th>PBS</th>
<th>CDDP/5-FU followed by ONYX-015</th>
<th>ONYX-015 with CDDP/5-FU</th>
<th>ONYX-015 followed by CDDP/5-FU</th>
<th>CR (%)</th>
</tr>
</thead>
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<td>PBS</td>
<td>22</td>
<td>NA</td>
<td>0.30</td>
<td>0.05</td>
<td>0.03</td>
<td>10</td>
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<tr>
<td>CDDP/5-FU alone</td>
<td>26</td>
<td>0.51</td>
<td>0.15</td>
<td>0.06</td>
<td>0.003</td>
<td>0</td>
</tr>
<tr>
<td>ONYX-015 alone</td>
<td>33</td>
<td>0.10</td>
<td>0.30</td>
<td>0.25</td>
<td>0.06</td>
<td>10</td>
</tr>
<tr>
<td>CDDP/5-FU followed by ONYX-015</td>
<td>33</td>
<td>0.30</td>
<td>NA</td>
<td>0.04</td>
<td>0.02</td>
<td>0</td>
</tr>
<tr>
<td>ONYX-015 with CDDP/5-FU</td>
<td>43</td>
<td>0.05</td>
<td>0.04</td>
<td>NA</td>
<td>0.40</td>
<td>20</td>
</tr>
<tr>
<td>ONYX-015 followed by CDDP/5-FU</td>
<td>47</td>
<td>0.03</td>
<td>0.02</td>
<td>0.40</td>
<td>NA</td>
<td>33</td>
</tr>
</tbody>
</table>

*a NA, not applicable.*

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**Table 2** Comparison of survival and complete response rates between treatment groups in the A2780/CP70 peritoneal carcinomatosis model

Monotherapy and concurrent therapy were given on days 12–16, whereas sequential treatments were given on days 12–16, followed by days 17–21. ONYX-015, cisplatin (CDDP), and 5-FU (5-fluorouracil) were administered i.p. as described in “Materials and Methods” (P = 0.06 and 0.08 for ONYX-015, followed by chemotherapy versus chemotherapy followed by ONYX-015).

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Alive at day 30 (%)</th>
<th>Complete responses (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBS</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>CDDP/5-FU alone</td>
<td>75</td>
<td>0</td>
</tr>
<tr>
<td>ONYX-015 alone</td>
<td>75</td>
<td>12</td>
</tr>
<tr>
<td>CDDP/5-FU followed by ONYX-015</td>
<td>75</td>
<td>12</td>
</tr>
<tr>
<td>ONYX-015 with CDDP/5-FU</td>
<td>88</td>
<td>25</td>
</tr>
<tr>
<td>ONYX-015 followed by CDDP/5-FU</td>
<td>100</td>
<td>38</td>
</tr>
</tbody>
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interaction with cisplatin-based chemotherapy. The superior results seen with virus prior to chemotherapy (versus the reverse) suggests a role for viral replication in the enhancement of chemosensitivity. Both infected and adjacent uninfected tumor cells may be sensitized to chemotherapy, although this remains to be proven. Potential mechanisms contributing to this interaction include E1A gene expression (occurring after ONYX-015 infection), which can augment both p53-dependent and p53-independent tumor cell killing (31–33). Another potential result of i.t. virus replication is the induction of chemosensitizing cytokines including TNF (34, 35). Deletion of the E3 region genes 10.4/14.5 and 14.7 leads to enhanced TNF induction and enhanced sensitivity of the infected cell to killing by TNF (35, 36); these genes are deleted in ONYX-015. The currently available animal models are limited in their ability to assess the contribution of the immune response to this interaction. Syngeneic immunocompetent and replication-permissive animal models have not been identified. Further animal model studies are under way with adenoviral constructs differing in their E1A and E3 regions in combination with cisplatin.

Novel locoregional therapeutic approaches are needed to improve the quality of life and survival of patients with relapsed head and neck and ovarian carcinomas. ONYX-015 has been well tolerated in Phase I and II trials after repeated direct intratumoral injections of head and neck tumors (25, 26) or i.p. administrations to ovarian cancer patients on a similar schedule.4 Despite encouraging biological effects, however, durable objective responses were not achieved in these patients. These tumors also frequently develop resistance to platinum-based chemotherapy.

A Phase II clinical trial of intratumoral ONYX-015 in combination with i.v. cisplatin and 5-FU has been completed recently in patients with recurrent head and neck cancer. Preliminary results mirror the encouraging activity described here (37); tumors receiving intratumoral ONYX-015 injections plus chemotherapy (i.p. 5-fluorouracil and cisplatin days 1–5) in one of three regimens: concurrent treatment (days 1–5), ONYX-015 (days 1–5) followed by chemotherapy (days 8–12), or chemotherapy (days 1–5) followed by ONYX-015 (days 8–12). A, tumor growth during study after chemotherapy followed by ONYX-015 ( ), concurrent ONYX-015, and chemotherapy ( ), or ONYX-015 followed by chemotherapy ( ). Bars, SE. B, Kaplan-Meier survival of animals following the same treatments (P = 0.02 for ONYX-015 followed by chemotherapy versus chemotherapy followed by ONYX-015).

Fig. 2 Single-agent versus combination treatment in the p53-functional A2780 ovarian peritoneal carcinomatosis model. To test the efficacy of combination treatment against tumor cells with functional p53, A2780 cells were injected into the peritoneal cavity of nude mice and were allowed to grow to an estimated tumor burden of 0.6 g (± 1.2). The effect of i.p. treatment on survival was evaluated for the following groups: ONYX-015 alone (•, 10⁶ pfu daily on treatment days 1–5), cisplatin alone (○, 4 mg/kg on treatment days 1, 3, 5), ONYX-015 and cisplatin (□, days 1–5 and 8, 10, 12, respectively), or neither treatment (○). All treatments were administered i.p., and there were 12 mice/treatment group. Combination treatment was superior to both no treatment control (P = 0.04) or either single-agent therapy (P = 0.07).

Fig. 3 Efficacy is dependent on the sequencing of chemotherapy and ONYX-015 in a nude mouse-human tumor xenograft model. Mice with s.c. HLaC flank tumors (9–10/ group) received ONYX-015 (i.t. 10⁶ plaque-forming units daily) plus chemotherapy (i.p. 5-fluorouracil and cisplatin days 1–5) in one of three regimens: concurrent treatment (days 1–5), ONYX-015 (days 1–5) followed by chemotherapy (days 8–12), or chemotherapy (days 1–5) followed by ONYX-015 (days 8–12). A, tumor growth during study after chemotherapy followed by ONYX-015 ( ), concurrent ONYX-015, and chemotherapy ( ), or ONYX-015 followed by chemotherapy ( ). Bars, SE. B, Kaplan-Meier survival of animals following the same treatments (P = 0.02 for ONYX-015 followed by chemotherapy versus chemotherapy followed by ONYX-015).
apeutic classes may have more or less of an effect on viral replication than cisplatin and 5-FU (38). The balance between enhanced sensitivity to killing by chemotherapy versus a potential inhibition of viral replication will have to be determined for each chemotherapeutic agent. In addition to this experience with a replication-selective adenovirus, replication-selective herpesviruses have also shown promise in combination with cisplatin-based chemotherapy (39). Combinations with radiotherapy are also being explored and look promising (40). Combination therapy with replication-selective oncolytic viruses and chemotherapy holds promise as a new cancer treatment paradigm.

REFERENCES


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