

Cancer immunotherapy via combining oncolytic virotherapy with chemotherapy: recent advances

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Abstract: Oncolytic viruses are multifunctional anticancer agents with huge clinical potential, and have recently passed the randomized Phase III clinical trial hurdle. Both wild-type and engineered viruses have been selected for targeting of specific cancers, to elicit cytotoxicity, and also to generate antitumor immunity. Single-agent oncolytic virotherapy treatments have resulted in modest effects in the clinic. There is increasing interest in their combination with cytotoxic agents, radiotherapy and immune-checkpoint inhibitors. Similarly to oncolytic viruses, the benefits of chemotherapeutic agents may be that they induce systemic antitumor immunity through the induction of immunogenic cell death of cancer cells. Combining these two treatment modalities has to date resulted in significant potential in vitro and in vivo synergies through various mechanisms without any apparent additional toxicities. Chemotherapy has been and will continue to be integral to the management of advanced cancers. This review therefore focuses on the potential for a number of common cytotoxic agents to be combined with clinically relevant oncolytic viruses. In many cases, this combined approach has already advanced to the clinical trial arena.

Keywords: oncolytic virotherapy, chemotherapy, immunogenic cell death

Introduction

The conventional cancer treatments of surgery, chemotherapy, and radiotherapy remain the mainstay of current therapeutic approaches to cancer. They have been used successfully in combination with one another in the neoadjuvant, concomitant, and adjuvant context for many years. However, despite their utility and curative potential, each modality has its limitations in terms of limited efficacy, significant toxicity, lack of durability of response, and in the case of chemotherapy the emergence of drug resistance. In addition to the release of neoantigens after tumor-cell destruction, exposure of cancer cells to cytotoxic agents may induce innate and adaptive immune responses against the cancer in other ways. Certain modes of cancer cell death are associated with immunogenicity through the induction of immunogenic cell-death (ICD) proteins, such as calreticulin, HSP70, ATP, and HMGB proteins.¹ A number of cytotoxic agents have been shown to induce ICD,² while others are capable of modulating the tumor microenvironment by reducing the function or number of suppressive immune cells (regulatory T cells [T_{regs}]³ and myeloid-derived suppressor cells [MDSCs]) or generating inflammatory cytokines (Table 1).^{3–137} Tumors treated with chemotherapy have also been shown to be more sensitive to cytotoxic T-lymphocyte (CTL) killing.⁵¹ Most of the evidence for ICD has been derived from murine models of human cancer. Relatively little is known about

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Table I Mechanisms of immunomodulation caused by chemotherapy (chemo) alone, and synergy seen when combined with oncolytic virus

| Chemotherapy drug | Mechanism of immunomodulation caused by chemo alone | Immunomodulation reference | Oncolytic virus-chemo synergy |
|-------------------|---|----------------------------|-------------------------------|
| Cyclophosphamide | Triggers TRAIL CD8 ⁺ T cell-mediated apoptosis | 3 | |
| | Induces proinflammatory production/induction of ICD marker calreticulin/HMGB1 | 4–6 | |
| | Decreased T _{reg} function | 7–9 | 10,11 |
| | CD8 ⁺ T cell-specific tumor activity | 7 | |
| | Induces T-helper type I or I7 immunity | 12 | 11 |
| | Decreases complement function | | 13 |
| | Suppression of immune cell types | | 14,15 |
| | Inhibits or delays viral neutralization response | | 14–23 |
| | Increases MDSCs | 24,25 | |
| | Enhances DC function | 26 | |
| | Synergy, but unknown immune function, if any | | 27,28 |
| Gemcitabine | Decreases MDSCs | 29 | 29–31 |
| | Decreases neutralizing antibodies | 29 | 29 |
| | Induces ICD marker calreticulin | 4 | |
| | Induces ICD marker HMGB1 | | 32,33 |
| | Depletes B cells | 34 | 35 |
| Bortezomib | Synergy, but unknown immune function, if any | | 32,36–45 |
| | Enhances DC function | 46 | |
| | ICD and DAMP release | 14 | |
| | Antitumoral immunity | | 47 |
| | CD8 ⁺ T cell-mediated inhibition of tumor growth | 46 | |
| Doxorubicin | Synergy, but undefined immune function, if any | | 48,49 |
| | Induces ICD marker calreticulin | 4 | 50 |
| | Granzyme B released by CTLs | 51 | |
| | Induces type I IFN response | 52 | |
| | Increases T _{reg} cells and significantly decreases NK cells | 53 | |
| Mitoxantrone | Decreases B7-H1/PD-L1 from cell surface | 54 | |
| | Synergy, but undefined immune function, if any | | 55–59 |
| | Induces DC/T-cell tumor infiltrate | 60 | |
| | Releases ATP | 60 | |
| | Ecto-CRT, ecto-HSP70, and HMGB1 | 61,62 | |
| Temozolomide | Tumor antigen-specific CD8 ⁺ and CD4 ⁺ T-cell activity | 60,63,64 | 65 |
| | Enhances DC function | 66 | |
| | Decreases T _{reg} function | 67 | |
| | Tumor-specific T-cell responses | 68 | 68 |
| | Synergy, but undefined immune function, if any | | 69–74 |
| Docetaxel | Decreases MDSCs, increases CD8 ⁺ T cells | 75 | |
| | Enhances DC function | 75 | |
| Paclitaxel | Synergy, but unknown immune function, if any | | 76–82 |
| | Granzyme B released by CTLs | 83 | |
| | Induces ICD marker calreticulin | 4 | |
| | Induces MHC | 84 | |
| | Decreases T _{reg} function | 85–87 | |
| 5-Fluorouracil | Induces T-helper type I immunity | 12 | |
| | Type I IFN and HMGB1 release in vitro | | 88 |
| | NK cells essential for strong synergy | | 10 |
| | Slows neutralizing antibodies (with carboplatin) | | 89 |
| | Synergy, but unknown immune function, if any | | 90–99 |
| Cisplatin | CD8 ⁺ T cell-mediated apoptosis | 100 | |
| | Induces carcinoembryonic antigen (CEA) | 101 | |
| | Decreases MDSCs | 102 | |
| Cisplatin | Synergy, but unknown immune function, if any | | 103–105 |
| | Decreases T _{reg} function | 106 | |
| | CD8 ⁺ T cell-specific tumor activity | 106 | |
| Cisplatin | Granzyme B released by CTL | 50 | |

(Continued)

Table 1 (Continued)

| Chemotherapy drug | Mechanism of immunomodulation caused by chemo alone | Immunomodulation reference | Oncolytic virus-chemo synergy |
|----------------------|---|----------------------------|-------------------------------|
| Mitomycin C | Enhances DC function, cytokine release, and cytotoxic T-cell activation | | 107 |
| | Synergy, but unknown immune function, if any | | 108–118 |
| | Enhances DC function | 71,119 | |
| Azadeoxycytidine | Synergy, but unknown immune function, if any | | 120–124 |
| | Enhances DC function | 71 | |
| Irinotecan | Decreases T _{reg} function | 125 | |
| | NK cells essential | 126 | 126 |
| Rapamycin/everolimus | Synergy, but unknown immune function, if any | | 126–129 |
| | Inhibition of T-cell proliferation | 130 | 131 |
| | Decreases DC maturation | 130 | |
| | Increases T _{reg} cells | 130 | |
| | Decreases cellular IFN | | 132 |
| | Decreases cytokine release | | 131 |
| | Decreases antiviral antibody production | | 131,133 |
| 5-Aza | Synergy, but unknown immune function, if any | | 132–136 |
| | Induces cancer testis antigen | 137 | |
| | Induces MHC | 137 | |

Abbreviations: ICD, immunogenic cell death; T_{reg}, regulatory T cell; MDSCs, myeloid-derived suppressor cells; DC, dendritic cell; DAMP, danger-associated molecular pattern; CTLs, cytotoxic T lymphocytes; NK, natural killer; MHC, major histocompatibility complex; TRAIL, TNF-related apoptosis inducing ligand; Ecto-CRT, ecto calreticulin.

the immunogenicity of chemotherapy in cancer patients. The combination of “immunogenic” or ICD-inducing chemotherapy with other anticancer treatment modalities capable of priming and/or propagating immune responses is now being evaluated. While the obvious candidates for combination are cancer vaccines, low doses of radiotherapy and immune-checkpoint inhibitors, there is an increasingly compelling case for combination of chemotherapy with oncolytic viruses (OVs).¹³⁸

Despite being recognized as having the potential to treat cancer since the beginning of the 20th century, OVs are only now entering the clinical arena for certain cancers, following the successful evaluation of talimogene laherparepvec (T-vec) in malignant melanoma.¹³⁹ OVs are live viruses that are selectively toxic to cancer cells. The basis of selectivity for cancer versus normal cells is based on cell entry (tumor cells expressing a receptor the virus uses to gain entry), impaired IFN response in cancer cells, or dysregulation in key signaling pathways, such as the RAS pathway, which would otherwise (eg, through the phosphorylation of PKR) allow the cell to negate the virus. Clinical trials involving OVs as single agents have largely been safe, demonstrated minimal toxicity, and in certain studies shown signs both of efficacy by radiological evaluation and the presence of live virus in tumor biopsies a week or more after treatment.^{140,141} However, the overall efficacy of single-agent OV therapy has at best been modest. The true potential of OVs may

yet be realized through their combination with other treatment modalities, such as chemotherapy. As well as synergistic mechanisms of tumor-cell killing, combination with chemotherapeutics through careful sequencing may help to overcome some of the barriers in the tumor microenvironment thought to limit the efficacy of OVs. These include large tumor size,¹⁴² poor vasculature,¹⁴³ elevated interstitial pressure,¹⁴⁴ and physical barriers.¹⁴⁵ One potential limitation of OVs that is regularly debated is the rapid generation of antiviral antibody responses a week or so following OV administration. There have been attempts to attenuate this response using such agents as cyclophosphamide (CPA; discussed later), but it is clear that despite high levels of neutralizing antibodies, further administrations of the same OV can traffic to the tumor environment and cause tumor kill. The OV is most likely protected from neutralizing antibodies by carriage (hitchhiking) on granulocytes, lymphocytes, and platelets to tumor cells in metastatic deposits.¹⁴⁶ Recent preclinical and clinical studies have shown that combining chemotherapy with OVs may potentially be highly synergistic, improving on the efficacy of each modality alone (Table 1).

In this review, we explore the many ways in which chemotherapy and OVs have been considered in combination. The methods used by researchers have been based on cell lines using classical isobologram analysis, murine models, and in humans with a number of completed clinical trials.

Cell-death mechanisms: immunogenic cell death is vital for cancer therapy

OV-mediated cell death does not fit exactly into one of the three classical categories of cell death (apoptosis, necrosis, and autophagy), and likewise cell-death pathways induced by chemotherapy can vary from agent to agent. Due to the physiological consequences associated with cell death, enormous effort has been invested into understanding the three main mechanisms. Apoptosis is vital for development and the maintenance of tissue homeostasis, and is generally considered to be a nonimmunogenic form of cell death, while necrosis, which is less coordinated and results in the release of proinflammatory cytokines, has been regarded as immunogenic.¹⁴⁷ However, it is now clear that the boundaries between each classical cell-death pathway are not defined and there is often overlap. This has been demonstrated by the discovery of “immunogenic” apoptosis in tumor cells, which can be induced by specific chemotherapies, such as the anthracyclines and oxaliplatin (Figure 1).^{148,149} Similarly, OV-mediated cell death does not fit into either apoptosis or necrosis, but displays features of both, with variations between oncolytic viral types. In general, the immunogenic death (apoptosis, necrosis, autophagy, etc) of

cancer cells involves a multistep process, beginning with the recognition of pathogen-associated molecular components, such as viral components, which cause such molecules as fractalkine, nucleotides, and ATP to be released, which in turn attract phagocytes or dendritic cells (DCs), and the expression of such signals as phosphatidylserine and calreticulin that aid recognition by phagocytes or DCs. Finally, danger-associated molecular patterns (DAMPs), such as HMGB1, are expressed. This enables dying tumor cells to lose the ability to induce tolerance and to stimulate powerful anticancer immune responses (Figure 1). Scientists have investigated many ways to increase the immunogenic effects seen with OVs, but it is becoming clearer that one way to complement the ICD mechanisms and the immunomodulatory effects (Table 1) seen with either therapy alone is to combine both OVs and chemotherapy to achieve either at least an additive or (even better) a synergistic result.

Combining chemotherapeutic drugs with OV therapy

Cyclophosphamide

CPA is an alkylating agent that causes cross-linking of DNA, and is used in the management of countless tumor types.

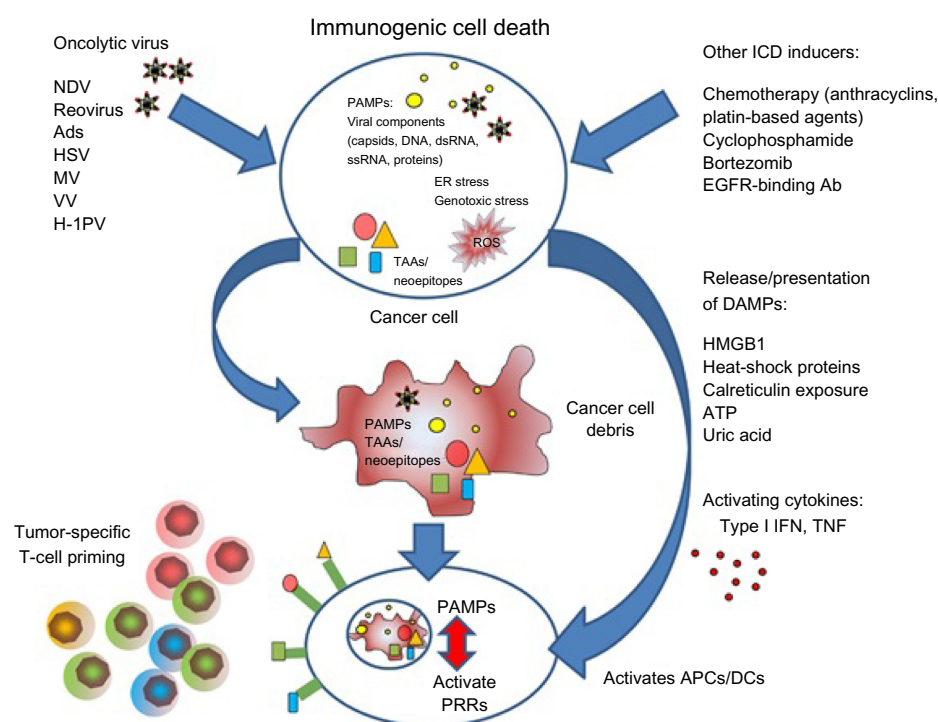


Figure 1 A summary of immunogenic cell death (ICD) caused by oncolytic virus and/or chemotherapy.

Note: Reproduced from Woller N, Gürlevik E, Ureche C-I, Schumacher A, Kühnel F. Oncolytic viruses as anticancer vaccines. *Front Oncol.* 2014;4:188. doi: 10.3389/fonc.2014.00188.¹⁴⁸

Abbreviations: Ads, adenoviruses; APCs, antigen-presenting cells; DAMPs, danger-associated molecular patterns; DCs, dendritic cells; dsRNA, double-stranded RNA; EGFR, epidermal growth factor receptor; ER, endoplasmic reticulum; HSV, herpes simplex virus; IFN, interferon; MV, measles virus; NDV, Newcastle disease virus; PAMPs, pathogen-associated molecular patterns; PRRs, pattern recognition receptors; PV, parvovirus; ROS, reactive oxygen species; ssRNA, single-stranded RNA; TAAs, tumor-associated antigens; TNF, tumor necrosis factor; VV, vaccinia virus.

In itself, CPA is not an active drug. It requires metabolic activation by aldehyde dehydrogenase, producing the active compound 4-hydroxycyclophosphamide. The release of HMGB1 and ecto-CRT is seen with CPA treatment, which results in DC activation, proinflammatory cytokine production, and T-cell proliferation.^{5,6} Synergy *in vivo* has been shown using a variety of OV and CPA, including herpes simplex virus (HSV)-1, adenovirus, vaccinia,^{27,28} reovirus, measles, myxoma virus,¹⁵ and vesicular stomatitis virus (VSV).²³ The combination of CPA with reovirus has been investigated in *in vivo* models, and these studies have demonstrated safety and efficacy using a carefully titrated CPA schedule, including administration 24 hours before reovirus.²⁰ However, significant normal-tissue toxicity was seen at higher doses, similar to the administration of reovirus to B-cell knockout mice.²⁰ Therefore, careful titration of any immunomodulatory effect is required to optimize efficacy without augmenting viral replication and toxicity in normal tissues. Studies with oncolytic HSV-1 and adenovirus in combination with CPA have shown a fall in the magnitudes of antiviral immune cells, which prevents, inhibits, or delays viral neutralization.^{14,17,19,21} CPA has been shown *in vivo* to deplete the complement response to HSV.¹³ With oncolytic measles virus and VSV, CPA has been shown to strongly damp down the antiviral host immune response,^{23,150} but in the case of a VSV combination resulted in reduced therapeutic efficacy compared to CPA alone.¹⁵⁰ Zemp et al showed that the removal of the tumor-resident macrophage population in an orthotopic glioma model by CPA substantially increased the survival of mice with myxoma virus post-treatment.¹⁵

Additional studies imply that a CPA/viral combination can also boost antitumor immunity by inhibiting T_{regs} .^{10,11} These data were confirmed in a Phase I clinical trial that showed that metronomic dosing of CPA decreased T_{regs} in solid tumors treated with adenovirus granulocyte macrophage colony-stimulating factor, without compromising the stimulation of antitumor responses.¹¹ In contrast, Phase I clinical trials showed that reovirus (where CPA dose was escalated from 25 to 1,000 mg/m²) or Seneca Valley virus coadministration with CPA were safe, but did not attenuate host antiviral responses.^{151,152}

Gemcitabine

Gemcitabine is a fluorinated deoxycytidine analog that has two forms: the gemcitabine diphosphate form, which impedes the ribonucleotide reductase enzyme, resulting in a reduction in the pool of deoxynucleotide available for DNA synthesis; whereas the second form, gemcitabine triphosphate, is incorporated into

DNA, causing chain termination and resulting in apoptosis and cell death. Gemcitabine has also been shown to deplete MDSCs and promote antitumor immune responses.¹⁵³ Both gemcitabine and CPA can decrease neutralizing antibodies in cancer patients.²⁹ An increase in antitumor activity was seen with a wide array of OV in combination with gemcitabine, including adenovirus,^{38–44} parvovirus,^{32,33} reovirus,^{30,37} VSV,³⁵ HSV,³¹ vaccinia,⁴⁵ and myxoma virus.³⁶ Gemcitabine alone fails to trigger HMGB1 release; in contrast, parvovirus does induce HMGB1.³² Combination treatment of both parvovirus and gemcitabine results in a high level of tumor cytotoxicity without impeding ICD activities.³²

In vivo studies with either HSV or reovirus in combination with gemcitabine improved the survival compared with either treatment alone.^{30,31} These therapeutic combinations also demonstrate that gemcitabine limits the reovirus/HSV-1-induced accumulation of MDSCs in the tumor microenvironment.^{30,31} Gemcitabine treatment in a Phase I clinical trial showed greatly reduced levels of reovirus-neutralizing antibodies, and 80% of patients exhibited either a partial response or stable disease.²⁹

Bortezomib

Bortezomib is a peptide-based, reversible proteasome inhibitor. Potent immunomediated antitumor effects were seen after treatment with bortezomib in the form of enhanced DC function and upregulation of the HSP60 and HSP90 proteins.⁴⁶ Bortezomib has been shown to generate reactive oxygen species, which are believed to cause ICD and DAMP release, increasing cellular stress.^{154–157} A number of OV have been studied in combination with bortezomib, including HSV-1,⁶⁰ reovirus,⁴⁹ adenovirus,⁴⁷ and VSV.⁴⁸ Both HSV-1 and reovirus have shown synergy, but the contribution of immunomodulatory effects of bortezomib and antitumor immune responses *in vivo* was not examined.^{49,156} Combining VSV and bortezomib resulted in antagonism *in vitro*, but in contrast synergy was seen *in vivo*.⁴⁸ This may have been due to immune cells *in vivo* that were not present in the *in vitro* setting. The authors of this study cited an ovarian tumor mouse study that showed reduction in tumor growth facilitated by CD8⁺ T-cell function with bortezomib alone.⁴⁶ In a hepatocellular carcinoma *in vivo* model, treatment with bortezomib and an adenovirus expressing human telomerase reverse-transcriptase resulted in caspase-dependent apoptosis and a reduction in the antiviral immune responses.⁴⁷

Doxorubicin

Doxorubicin (Dox) is an anthracycline antibiotic that intercalates into the DNA double-helical structure. This

intercalation process hinders unwinding and resealing of DNA for transcription, and thus inhibits cellular DNA replication. Dox also stimulates the rapid production of type I IFNs by tumor cells after activation of TLR3, resulting in the release of chemokine (CXCL10).⁵² A type I IFN gene signature-predicted response to Dox therapy has been seen in breast cancer patients.⁵²

These data suggest that Dox-mediated immune responses mimic those induced by viral pathogens. In addition to inducing ICD⁴ and type I IFN secretion, Dox and other chemotherapeutics also increase the susceptibility of tumors to CTLs by increasing tumor-cell permeability to granzyme B released by the CTLs.⁵¹ The addition of Dox to adenovirus resulted in significantly increased expression of calreticulin in vitro.⁵⁰ Synergy between Dox and other OV, such as HSV-1,⁵⁵ measles,⁵⁶ vaccinia,⁵⁷ Coxsackie virus 21,⁵⁰ and VSV59 has been seen in vitro and in vivo, but no immunocomponent effects have yet been defined.

Mitoxantrone

Mitoxantrone (MTX) is a synthetic anthracenedione antineoplastic agent derived from the anthraquinone dye ametantrone,¹⁵⁸ which is frequently used to manage prostate, leukemia, and breast cancer.^{159,160} It is structurally similar to Dox, with both drugs having a planar aromatic ring structure that enables them to interact with DNA by intercalation between base pairs. MTX can inhibit the activity of the nuclear enzyme DNA topoisomerase (II), interfere with RNA and cause the cross-linking of DNA and strand breaks, and produce reactive oxygen species. MTX is believed to lack cell-cycle phase specificity, because it has cytotoxic effects on both proliferating and nonproliferating cells.¹⁶¹ MTX also has immunosuppressive properties, resulting in the inhibition of proinflammatory cytokines, such as TNF, IL-2, and IFN γ . It is therefore used in the management of multiple sclerosis.¹⁶² Cancer cells undergoing immunogenic apoptosis and autophagy after treatment with MTX express various DAMPs, such as ecto-HSP70, ATP, and HMGB-1,^{160,161} and stimulate the peripheral relocation of CRT.¹⁶³ MTX treatment also increases uptake of tumor-associated antigens by antigen-presenting cells, resulting in establishment of antitumor activity by antigen-specific CD8⁺ and CD4⁺ T cells.^{59,63,64} Both in murine models^{76,77} and in human patients with cancer,¹⁴⁶ antitumor immune responses induced by cancer cells undergoing ICD are associated with better clinical responses. A combination of HSV-1 with MTX failed to increase cytotoxicity or halt virus replication in vitro.^{65,164} In contrast, in vivo, the same combination provided significant survival benefit when administered locally to HER-2/*neu*

subcutaneous tumors.⁶⁵ This protective effect was facilitated by enhanced levels of tumor antigen-specific CTL cells and an increase in intratumoral infiltration of neutrophil cells.⁶⁵ These results were confirmed by depleting CD4⁺, CD8⁺, and Ly6G-expressing cells from the model, showing that these cells are essential for enhanced efficacy.⁶⁵

Irinotecan

Irinotecan is an antineoplastic enzyme inhibitor and shows activity against colorectal, lung, esophageal, and gastric cancers, leukemia, and lymphomas. Irinotecan inhibits the topoisomerase I-DNA complex and causes double-strand DNA breakage that results in cell death. In the clinic, irinotecan is used in combination with fluorouracil and leucovorin (FOLFIRI) in colon cancer patients.¹²⁵ Treatment with the FOLFIRI combination significantly reduced the amount of CD4⁺FoxP3⁺T_{regs} in patients, without altering the total number of lymphocytes or the population of CD4⁺ T lymphocytes.¹²⁵ Irinotecan has been shown to inhibit HSV-1 viral replication and lytic oncolysis in colon cancer cell lines.¹⁶⁴ In contrast, other groups show synergy with OV/irinotecan, including HSV-1 encoding CYP2B1,¹²⁷ reovirus,¹²⁸ and Sindbis virus.¹²⁶ However, only the study on Sindbis virus looked at immune components in irinotecan synergy, concluding that natural killer cells are essential for the process.¹²⁶

Temozolomide

Temozolomide (TMZ) is an alkylating agent currently used as first-line therapy for glioma treatment, due to its DNA-damaging effect.^{165,166} Advanced melanoma patients treated with low-dose TMZ followed by DC (autologous tumor lysate) vaccination showed a reduction in circulating immunosuppressive FoxP3⁺T_{regs}.⁶⁷

Synergy has been recorded between TMZ and both HSV^{69,71} and adenovirus.^{68,72–74} An unconventional patient study on various cancers treated with oncolytic adenovirus and a low dose of TMZ showed an upregulation of ICD signal HMGB1 and specific tumor T-cell responses, which resulted in disease control in 67%⁶⁸ of cases. These results are interesting, but are difficult to interpret, due to the large number of different types of adenoviruses used in this study and differences in doses of TMZ.

PI3K–Akt–mTOR pathway inhibitors

The PI3K–Akt–mTOR signaling cascade is well characterized and plays a crucial role in a variety of physiologic processes, including cell-cycle progression, differentiation, transcription, translation, apoptosis, motility, autophagy, anabolic processes (including protein and lipid synthesis), and metabolic

processes (including normal glucose homeostasis). Activation of the PI3k–Akt–mTOR signaling pathway is implicated in tumorigenesis, and PI3K–Akt–mTOR is the most frequently mutated pathway in cancer. PI3K/Akt inhibitors show synergy with HSV-MG18L71 and adenovirus ZD55-TRAIL166, but immunocomponents were not studied. mTOR is a master regulator of cellular translation and also impacts translation of viral proteins. Rapamycin is able to inhibit mTOR^{167,168} by forming a complex with FKBP12.^{141,169} This inhibits proliferation, which results in the induction of autophagy in cancer cells.^{130,170} T and B lymphocytes also show a decrease in cell function in the presence of rapamycin.^{171–175} Also, rapamycin exhibits significant antiangiogenesis and anticancer properties.¹³³ Studies with an oncolytic HSV show that rapamycin enhances viral replication in vitro.¹³⁴ A possible mechanism for this enhanced viral replication may be the reduction of cellular IFN, which has been seen with VSV/rapamycin in an in vivo glioma model.¹³⁶ Studies with adenovirus have shown that rapamycin/everolimus can suppress the adenovirus innate response (TNF, IL-1 β , IL-6, IL-8, IL-10, IL-12, and IFN δ) reduce T-cell infiltration and decrease anti-Ad antibody production and T-cell function.^{131,133} This suppression by rapamycin/everolimus of the host viral immune response may explain the improved efficacy of oncolytic HSV,¹³⁴ VSV,¹³⁶ adenovirus,^{131,135} and myxoma virus¹⁵ in a number of in vivo models.

Mitomycin C

Mitomycins are a group of antineoplastic antibiotics, of which mitomycin C (MMC) is the most studied. MMC is an alkylating agent that cross-links DNA and is produced by *Streptomyces caespitosus*. Apoptosis can be induced by MMC, either by the caspase 3- and 8-dependent Fas–FasL pathway or via the activity of the NF κ B pathway.¹⁷⁶ MMC has also been shown to maintain innate and adaptive immune responses in a major subpopulation of human blood DCs (slan DC). This has encouraged the design of clinical trials for tumor patients that are based on the simultaneous administration of tumor antigen-loaded DCs and MMC.¹¹⁹ Intracellular adhesion molecule-1 and decay accelerating factor, the viral entry receptors for Coxsackie virus A21, have been shown to be upregulated in the presence of MMC, leading to synergy between virus and drug.¹²⁰ HSV-1,^{121–123} vaccinia,¹²⁴ and adenovirus¹⁷⁷ have all shown synergy with MMC, but these studies have not identified any immune-function mechanism.

Docetaxel

Docetaxel (Doc) has been shown to have a number of inhibitory functions on tumor cells, including inducing apoptosis,

angiogenesis, and impeding gene-expression processes,¹⁷⁸ but its primary anticancer function is via microtubule stabilization. Doc has been shown to decrease MDSCs and thus increase CD8⁺ T-cell activity in a murine model of breast cancer.¹⁷⁹ Oncolytic adenovirus,^{76–79} reovirus,^{80,81} and HSV-1⁸² have all shown synergy with Doc, but these studies have not identified any immune-function mechanism. Doc had no effect on the production of neutralizing antibodies to reovirus in a Phase I clinical trial.⁸¹

5-Fluorouracil

5-Fluorouracil (5-FU) is an antimetabolite drug that inhibits the enzyme thymidylate synthase and the incorporation of its metabolites into RNA and DNA.¹⁸⁰ 5-FU did not suppress the production of neutralizing antibodies against G207, but increased viral spread in subcutaneous hamster gallbladder tumors.¹⁰⁵ Antitumor effects of 5-FU are mediated, at least in part, by its selective cytotoxic action on MDSCs.¹⁰² Exposure of colon and pancreatic cancer cells to 5-FU significantly antagonizes both wild-type HSV-1 replication and lytic oncolysis.¹⁶⁴ In contrast, an HSV-1 mutant missing one copy of its ICP0, ICP4, and ICP34.5 gene (NV1066) resulted in enhanced viral replication.

Cisplatin

Cisplatin is a well-characterized alkylating agent used for the management of a wide range of cancers. As with other alkylating agents, its main mode of action is its ability to cross-link with the purine bases on the DNA. Cisplatin also interferes with DNA-repair mechanisms, which causes DNA damage, and subsequently induces apoptosis in tumor cells.¹⁸¹ Cisplatin can decrease T_{regs} and enhance antigen-specific CD8⁺ T-cell activity in murine models,¹⁰⁶ and almost completely abrogate the inflammatory cytokine gene upregulation induced by reovirus.¹¹⁵ In contrast, a parvovirus–cisplatin combination induced higher cytokine release than either agent alone, and also resulted in pronounced DC maturation and cytotoxic T-cell activation.¹⁰⁷

Discussion

OVs have been shown to be safely combined with conventional cytotoxic agents and evaluation in clinical trials justified on the basis of potential synergy through direct cytotoxicity, indirect immunogenicity, and/or alteration of the tumor microenvironment. The number of agents in clinical trials reflects the potential for this approach, which has recently focused away from delivery of live viruses to tumor sites, tumor lysis, and debulking to the induction of antitumor immunity through local induction of ICD, which ultimately will result in abscopal

effects on distant metastases. Although not yet formally addressed in studies, there would most likely be low likelihood of cross-resistance to either treatment modality.

A number of human studies have already exploited this potential, as exemplified by the US Food and Drug Administration approval of the agent T-Vec for the treatment of malignant melanoma. Ongoing human studies are evaluating both DNA and RNA viruses and wild-type agents, as well as modified agents expressing immunostimulatory gene products. Combination with immune-checkpoint inhibitors has swiftly followed, with signals already of increased response rates compared to virus or checkpoint inhibitor alone.¹⁸² This follows evidence in a preclinical in vivo melanoma model, the oncolytic Newcastle disease virus, in combination with an anti-CTLA-4 antibody (ipilimumab), that showed enhanced tumor infiltration by activated CD8⁺ and CD4⁺ T cells and a reduction in T_{regs}.¹⁸³ This model also showed a nearly 70% rate of cure with combination treatment compared to less than 25% for agents alone. Prolonged survival was also seen in the same in vivo melanoma model (B16.F10) when treated with a combination of anti PD-1 antibody and reovirus.¹⁸⁴ It is most likely that in the near future, combination studies with OV's will focus largely on immune-checkpoint modulation, but this may be tempered in term of toxicities and high cost.

While the earliest combination studies of OV's with chemotherapeutic agents were focused on attenuation of the expected brisk neutralizing antiviral antibody response, there is huge potential for combinations based on the immunostimulatory effects of common cytotoxic agents. Recent studies have shown convincingly that many OV's can hitchhike on circulating blood cells, are protected from neutralizing antibodies, and reach tumor sites, so this end point of chemotherapy–OV combination is now being considered less important. A key factor that may allow combination studies to evolve is that almost all human OV studies have been associated with minimal toxicity, and actual dose-limiting toxicities rarely achieved. Therefore, patients will not be expected to face new and additional side effects and lower quality of life beyond the known chemotherapeutic agent-toxicity profile.

Historically, chemotherapy has been thought to prompt cancer cell death in an immunogenically silent way, but extensive studies have shown that such treatment can induce humoral and cellular antitumor immunity and break immune tolerance to tumors. The more subtle detail of this potential centers around the dose and sequencing of agents: CPA is myelosuppressive at conventional doses, but immunomodulatory as a single dose in combination with

immunotherapy, or may be used to delete T_{regs} by metronomic dosing. Furthermore, combination studies will logically exploit the natural tropism of certain OV's for tumor vasculature with chemotherapeutic agents with antiangiogenic potential or those that may cause vascular leakage to allow OV into that tumor microenvironment.¹⁸⁵

There is huge potential for the combination of OV's with chemotherapeutics, but success will entail careful selection of the OV, the tumor model, the molecular dysregulation harbored by the malignancy, and the transgenes the OV carries, together with the best dose and sequencing with the most appropriate cytotoxic. The ideal disease setting and virus is not clear as yet, and further challenges will be evaluation of response to combination therapy and the contribution of an OV added to a classical three-drug regimen in a common setting, such as advanced breast or gastrointestinal cancers. Our wealth of experience with single- and multiagent chemotherapy regimens at least allows us a head start with clinical translation of combinations with OV's.

Disclosure

The authors report no conflicts of interest in this work.

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