Improved Antitumor Effect of Adenovirus-Mediated Interferon Therapy in Combination with Chemoradiotherapy in a Synergic Immunocompetent Hamster Model

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Abstract

While the emergence of advanced interventional (IFN) alpha-based clinical studies as a potential treatment strategy for pancreatic adenocarcinoma (PDA), the efficacy and insufficiency of IFN in tumor regression or patient survival remain under debate. The major concerns interfering the potential clinical utility of IFN therapy are the lack of a systemic expression of IFN in adenovirus-producing hamster pancreatic cancer xenografts and the low concentration of IFN induced in the tumor itself. Moreover, the combination of IFN with chemotherapy or radiation therapy is still insufficient for the systemic expression of antitumor effects. We report herein improved antitumor effect of adenovirus-mediated IFN in combination with radiation therapy in a hamster pancreatic adenocarcinoma model through the overexpression of bromodeoxyuridine (BDR) in adenovirus-producing hamster cells. The improved antitumor effect was associated with increased IFN expression in the tumor, improved cytolysis in hamster pancreatic cancer cells, and increased survival of animals in vivo compared to controls. IFN combined with the injection of radionuclide progeny centered in the tumor significantly improved survival. These findings suggest that the combination of IFN and radiation therapy may be an effective therapeutic strategy for pancreatic adenocarcinoma.

IFNα-based Adjuvant Chemoradiation Therapy Could Be a Powerful Tool for Pancreatic Adenocarcinoma

- Virginia Mason Medical Center: an improved 5-year survival rate of 55% in a phase II trial evaluating adjuvant chemotherapy, immunotherapy and adjuvant radiation (Rossi et al., Am J Surg 2019).
- Washington University Medical Center: Phase III trial resulted in 50% 2-year survival (Lineman et al, Ann Surg 2008).
- University of Heidelberg, Germany: Phase III trial for adjuvant treatment of pancreatic adenocarcinoma, the first immunomonitoring data (Schmoll et al, JAMA 2007).

Major Concerns Impairing the Clinical Utility of IFNα:

1. Systemic toxicity of IFNα
2. Insufficient delivery and unsustainable levels of IFNα in the tumor site

Conditionally Replicating Adenovirus (CRAd) Expressing IFNα

- CRAds express syngeneic IFNα. The IFNα gene is linked to the Ad major late promoter.
- AdE3C promoter is controlled by CRAd promoter.
- AdE3C expresses IFNα in vivo through fiber modification and over-expression of adenoviral death protein (ADP).
- IFNα-induced IFNα signaling is mechanistically different from the IFNα-induced antitumor effect in vitro and in vivo.
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Comparison of Syngeneic IFNα Biological Activity in Two Different Cancer Models

- Immune-deficient NCr nude mice
- Immune-competent Syrian hamsters
- Human xenografts
- Hamster xenografts
- AdE3C-IFNα
- Ad hamE3C-IFNα

- Ability to establish human cancer xenografts
- Does not permit human Ad replication
- Impossibly to induce immune response
- Hamster tumor only
- Retains human Ad replication
- Ability to analyze immuno-surveillance effect of IFNα-expressing Ad

In Vivo Combination Therapy with Radiation (200Gy)

- Combination therapy was significantly superior to either monotherapies
- Combination therapy outperformed all dual therapy treatments

In Vivo Combination Therapy with Radiation (80Gy) and SFU

- Combination of RG203 hamE3C-IFNα and radiation was superior to radiation and chemotherapy in combination of RG203 hamE3C-IFNα and radiation.
- Radiation therapy outperformed all dual therapy groups

In Vivo Combination Therapy with Radiation (80Gy) and SFU

- Radiation therapy outperformed all dual therapy groups

Improved Survival Rate with Combination Therapies

- The evaluation of the survival rate showed great improvement in groups treated with dual (RG203 hamE3C-IFNα+Rad8 Gy) and triple therapies.

Summary

1. IFNα-expressing oncolytic Ad exhibits multiple, integrated antitumor effect.
2. IFNα-expressing oncolytic Ad sensitizes chemotherapeutic and radiotherapy.
3. Infection-enhanced, tumor-selective oncolytic adenovirus expressing syngeneic IFNα is a promising therapeutic modality for pancreatic cancer.

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Contributors

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