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Chemo-sensitization and immunological reactions to HyperAcute™ Immunotherapy, a novel approach to cancer treatment

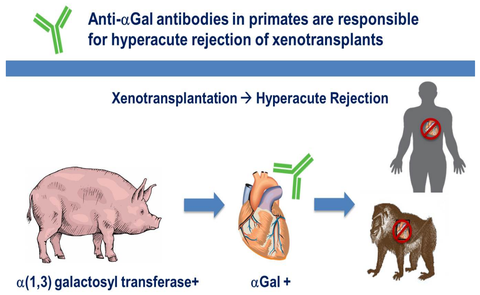
John C. Morris[1], Gabriela R. Rossi[2], Caio Max S. Roche Lima[3], Lucinda Tennant[2], W. Jay Ramsey[2], Eugene Kennedy[2], Nicholas N. Vahanian[2] and Charles J. Link[2]

[1]University of Cincinnati, Cincinnati, OH; [2]NewLink Genetics, Ames, IA; [3]University of Miami, Miami, FL

Background

Long term survival rates for most solid tumors have remained relatively constant over the past decade, with improvements being primarily incremental. Immunotherapy for the treatment of cancer has gained increasing prominence in recent years due to the proven success of several approaches. HyperAcute™ cancer immunotherapies consist of genetically modified irradiated allogeneic tumor cells expressing αGal moieties that stimulate the development of immunity directed against antigens shared by immunotherapy cells and host tumors. This technology is based upon the Hyperacute rejection seen in higher primates, a well-characterized potent innate immune defense mechanism by which antibodies directed against alpha(1, 3)-Galactosyl carbohydrate epitopes leads to the rapid destruction of xenografts and zoonotic agents from lower mammals. Drugs of this class have been used in clinical trials with promising results in DFS, OS, tumor responses and correlative immunological data. Immunotherapy has the potential to increase sensitivity of cancer cells to chemotherapy (1,2). Here we report potential chemo-sensitization effects of HyperAcute immunotherapy across multiple diseases as well as additional intriguing immunological responses.

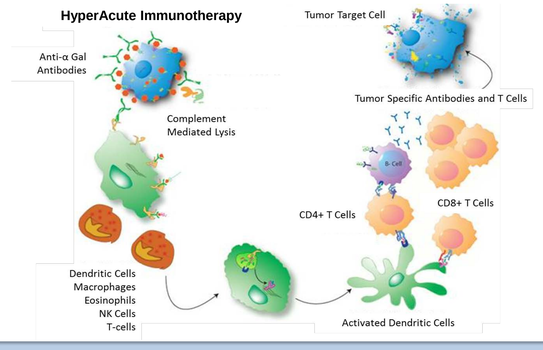
Figure 1



- The α(1,3)galactosyltransferase (αGT) gene is expressed by lower mammals, but not in humans or other Old World primates (3,4)
- Humans naturally acquire anti-αGal antibodies to levels that can reach 1% of total circulating antibodies (3,4)
- Anti-αGal antibodies responsible for HyperAcute rejection of xenotransplants (Fig 1)(4)
- Animal models demonstrate anti-tumor efficacy when αGal expressing tumor cells are utilized as immunotherapies (5,6,7)

Figure 2

Mechanism of action for HyperAcute immunotherapy which consists of stably transduced human cancer cell lines expressing the murine αGT gene



Objectives

Primary

- Assess objective tumor response to follow-on chemotherapy after HyperAcute immunotherapy

Secondary

- Evaluate immunological responses to HyperAcute immunotherapy

Methods

Clinical Trials

- Over 500 patients have received HyperAcute immunotherapy in clinical trials to date
- Results reported here were obtained from 122 patients treated in the three Phase 2 trials listed below (Table 1)
- Immunological correlates were assessed in all three trials
- Patients with tumor progression on study were monitored for response to subsequent salvage chemotherapy

Table 1

Indication	Immunotherapy	Patients (n)	1 Year Survival
Resected pancreas	Algenpantucel-L + Chemoradiation	69	86%
Advanced NSCLC	Tergenpumatucel-L	28	46%
Advanced melanoma	HyperAcute-Melanoma (HAM) + peg-intron	25	63%

Results

Clinical Response Summary Resected Pancreas

- Primary endpoint: 1- year DFS was 62% (p=0.02, 14.1 month median DFS)
- Secondary endpoint: OS at 12 months was 86% (24.1 month median OS)

Clinical Response Summary Advanced Lung

- 11.3 month median overall survival (95% CI 3.8-21.9)
- 46% one year survival
- 8 patients (29%) achieved stable disease (SD) ≥4 months
- 31% ORR (5/16) to subsequent chemotherapy

Clinical Response Summary Advanced Melanoma

- Median OS 19 months

Safety

- Well tolerated. No treatment related SAE's
- Common AE's included localized skin reactions, fatigue

Potential Chemo-sensitization Algenpantucel-L

- Three pancreatic cancer patients developed recurrent disease after algenpantucel-L therapy
- Subsequently they received FOLFIRINOX, gemcitabine + capecitabine + erlotinib, or gemcitabine + docetaxel
- Interestingly, all 3 patients experienced durable (12-36M), complete responses (CR)

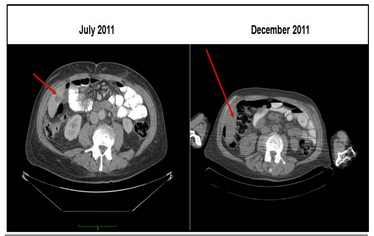


Figure 3. Case report #1 . Patient treated with algenpantucel-L 4 mos before recurrence (liver mets by CT/PET and elevated CA19-9). Subsequent treatment: FOLFIRINOX with complete radiologic (CT/PET) and biochemical response.

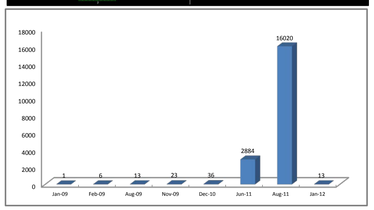


Figure 4. Case report #2. Patient w/ rapid rise of CA-19-9 18 months after diagnosis and recurrence confirmed by CT/PET. The patient achieved CR after Gem/ Xeloda/ Tarceva, confirmed by CT/PET and CA 19-9.

Potential Chemo-sensitization Tergenpumatucel-L

- Patients were followed for response to subsequent treatment after progressing on tergenpumatucel-L (table 2)
- 16 patients that progressed received salvage chemotherapy
  - 5/16 (31%) achieved partial response
  - 4/16 (25%) achieved stable disease

Table 2

Response	Patients (n)	Rate (%)
Partial Response	5	31%
Stable Disease	4	25%
Progressive Disease	7	44%

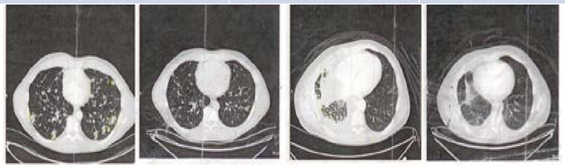


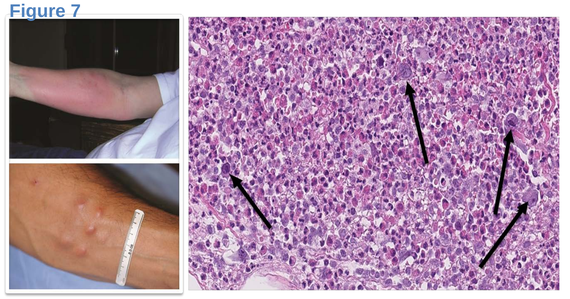
Figure 5. Case report #1 Patient 036 received subsequent chemotherapy and had a durable partial response. Patient survived 3 years after initial progression in the trial.

Figure 6. Case report #2 Patient 041 received subsequent chemotherapy and experienced rapid partial response. Patient survived 16 months after initial progression in the trial.

Immunological Responses- Skin (Fig 7)

- Injection site reactions of wheal & flare to DTH response
- Recrudescent flares at distant previously vaccinated sites up to one year after treatment
- Eosinophilic infiltrates at injection sites

Figure 7



Immunological Responses Algenpantucel-L

- Anti-CEA, Anti-αgal and/or Anti-mesothelin antibody increases correlated with improved survival
- Peripheral eosinophilia in 70% of treated patients

Immunological Responses Tergenpumatucel-L

- Increased numbers of tumor specific T-cells producing interferon-gamma correlated with improved survival in NSCLC patients

Immunological Responses HyperAcute Melanoma

- All patients tested (24/24) seroconverted with the development of autoimmune antibodies (anti-cardiolipin, anti-thyroglobulin, or both) after treatment
- After treatment vitiligo developed in 4/12 patients, correlating with 2 patients who underwent complete tumor regression

Conclusions

HyperAcute Immunotherapy

- Promising responses to follow-on chemotherapy after vaccination is suggestive of chemosensitization
- Observations being followed up in phase 3 in 722 resected pancreas cancer patient trial and a phase 2b/3 NSCLC trial (open for accrual)
- Immunologic data suggests HyperAcute immunotherapy elicits anti-cancer responses

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