Combination treatment of immune primer ilixadencel with standard therapy known to inhibit immunosuppression: a case report.

Magnus Rizell [1], Malin Sternby Eilard [1], Bengt Andersson [2], Peter Suenaert [3], Alex Karlsson-Parra [3,4]

[1]Transplant Institute, Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden; [2]Department of Clinical Immunology, University of Gothenburg, Gothenburg, Sweden; [3]Immunicum AB (Sponsor), Gothenburg, Sweden; [4]Department of Immunology, Genetics and Pathology, Uppsala University, Uppsala, Sweden.

Abstract

Objective: Present a patient case with advanced intrahepatic cholangiocarcinoma (CC) showing exceptional survival after combination of the immune primer ilixadencel with standard drugs known to induce immunogenic cell death and inhibit tumor-derived immunosuppression.

Methods: A 65 years old male patient with CC, metastasized to the lungs at diagnosis and with ECOG 1, anemia and hypo-albuminemia at enrollment received three intratumoral administrations (day 1,15 and 46) of the immune primer ilixadencel, consisting of allogeneic pro-inflammatory dendritic cells (DCs) aimed to locally recruit and activate endogenous DCs within the treated liver lesions. Ilixadencel was administered the day after transarterial chemo-embolization (TACE) with doxorubicin-eluting microspheres, aimed at inducing immunogenic tumor-cell death (1) within the ilixadencel-treated tumor lesion. The actual CC patient was included by an amendment in a recently completed clinical study in liver cancer patients (NCT01974661).

Results: The combined treatment with TACE + ilixadencel was associated with transient fever reactions without any other ilixadencel-related AEs. As to immunological parameters, the frequency of IFN-gamma producing CD8+ T cells in peripheral blood (against hTERT and AFP) was increased 1 week after the third dose of ilixadencel when compared to baseline levels. Three months after start of treatment hemoglobin and albumin levels were normalized and computer tomography (CT) showed partial response according to modified RECIST. At 6 months, however, the tumor progressed despite slight improvement of overall quality of life (EORTC QLQ-C30). Standard gemcitabine/cisplatin (G/C) regimen was started and resulted again in a partial tumor response. Due to drug intolerance G/C was stopped and leptomeningeal carcinomatosis developed 15 months post start of G/C . With whole brain radiotherapy alone patient survived for another 19 months with acceptable quality of life, which results in an overall survival of 41 months.

Conclusion: We hypothesize that combination of ilixadencel-induced recruitment and activation of endogenous DCs, local doxorubicin-induced immunogenic cell death (1) as well as the addition of gemcitabine that is known to deplete myeloid-derived suppressor cells (2), may act in synergy as indicated by objective tumor response and prolonged survival.

Introduction

- Reported incidence of CC in the US is one or two cases per 100 000 population.
- Due to the often locally advanced presentation, this disease is still associated with high mortality.
- Therefore, innovative approaches are welcome.

On Study

This subject was included in the IM-102 study, a prospective single arm, open label phase I study in subjects with advanced hepatocellular carcinoma (HCC) (ClinicalTrials.gov, NCT01525017). Study primary endpoint was safety and secondary endpoints included immunological response and clinical activity. Seventeen HCC patients were included in the immunological and safety sets. After an amendment in the study protocol one patient with bile duct cancer was also included.

The bile duct cancer patient received three doses of 10 million cells of ilixadencel administered intratumorally in a liver lesion under ultrasonic guidance.

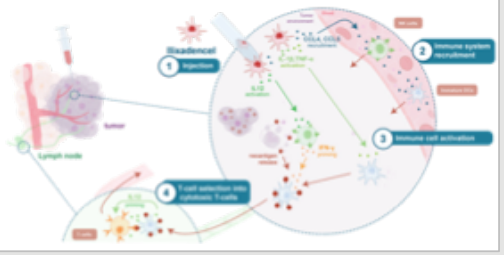
Measurements:

- Safety & auto-immunity
- Detection of tumor-specific CD8+ T cells
- Objective Response by modified RECIST and RECIST v1.1
- Quality of Life (EORTC QLQ-C30 questionnaire)
- Survival

Proposed Mechanism of Action by ilixadencel

→ priming of patient's immune system

Allogeneic dendritic cells (*ilixadencel*) are activated to secrete high amounts of chemokines and cytokines that recruit and activate patient's own DCs and NK cells, and these activated DCs capture tumor-specific neoantigens and subsequently prime CD8+ T cells towards a Th1-polarized cytotoxic immune response (3,4).

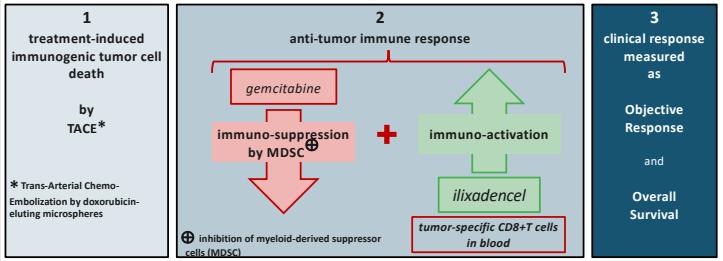


Sequence of Events

Treatment with TACE	@day0	
Male, 65y, med Hx non significant intrahepatic cholangiocarcinoma with lung metastases (right) – stage T2N0M1 ECOG 1		
Treatment with ilixadencel #1	@day1	no dose-limiting toxicity
		related adverse events:
Treatment with TACE	@day14	
Treatment with ilixadencel #2	@day15	- fever (moderate)
Treatment with TACE	@day45	
Treatment with ilixadencel #3	@day46	
Increased systemic anti-AFP and anti-hTERT CD8+ T cells (peripheral blood)		
	@3M	Imaging: partial response per mRECIST
QoL slightly better	@6M	Imaging: progression per mRECIST
Start of gemcitabine/cisplatin doublet chemotherapy	@9M	Imaging: partial response per mRECIST
Development of intolerance for G/C	@14M	Imaging: stable disease per mRECIST
	@17M	
	@21M	Tumor progression: leptomeningeal carcinomatosis
Treatment by whole brain radiotherapy		
Death	@41M	

Treatment Strategy

based upon immune-mediated hypothesis:



Conclusion & Hypothesis

- **We report an exceptionally long survival of a subject with metastatic cholangiocarcinoma who was treated by a combination of allogeneic cell-based immunotherapy with locoregional and systemic chemotherapy and brain radiotherapy.**
- **We hypothesize that combined treatment modalities with complementary immune-mediated mechanistic actions generate a synergistic clinical effect.**

References

1. Suzuki E. et al. Clin Cancer Res 2005;11:6713
2. Casares et al. J Exp Med 2005;202:1691
3. Fotaki et al. Oncoimmunology 2017;e1395126
4. Laurell et al. Journal for ImmunoTherapy of Cancer 2017;5:52