Adenoviral gene therapy for osteosarcoma

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Introduction

Gene-based therapy has emerged as a potentially powerful therapeutic platform, and in 64.3% of cases, indications addressed by this tool are for cancer diseases. Osteosarcoma is one of the most common, nonhematologic primary bone tumours. Most patients have no specific clinical symptoms, however, when present, the most frequent symptom is pain, usually present several weeks or months prior to diagnosis. The most frequent presenting clinical sign is a firm and tender mass, often brought to attention to by a minor trauma. Next to the tumour in the musculoskeletal system, lung metastasis eventually causes the patient's death in the vast majority of cases which develop metastatic disease. One of the most widely used vectors in cancer gene therapy (23.2%), is the adenoviral vector, which offers advantages such as growing to high titers and capability of infecting a variety of cells in different tissues. This review is focused on the aspects that gene therapy using adenovirus has evolved so far, chiefly directed to the treatment of osteosarcoma.

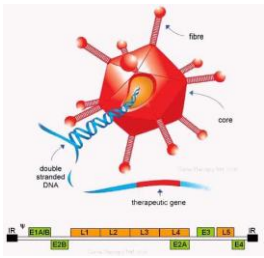


***Fig 1**. Adenoviral particle and its genome organisation. Extracted from <genetherapynet.com>*

Adenovirus gene therapy

Adenoviruses (Ad) are DNA-containing non-enveloped viruses. The ability of adenovirus to be grown to a high titer and to engage in high-level heterologous gene expression has made human adenovirus popular gene therapy vectors. Below, a number of developments in the subject of the review are summarized.

Gene therapy	Ad Vector Modification	Obstacles	Target	Clinical stage	Mechanisms	Results	Trial organism
Tumour suppressor gene dysfunction	pRb and p16INK4A	Less effective in the presence of functional pRb in cancer cells.	pRb null tumour cells	Preclinical	Restoration of pRb.	Supress tumorigenicity	Nude mice
	p53 (p53VPΔ30)	No clearance of the tumour.	Transformed cells	Preclinical	Accumulation of p53VPΔ30, regardless of endogenous p53 and Mdm2 status.	Induction apoptosis	Nude mice
Transductional targeting	Ad-D24-RGD and Ad-RGD-D24-GMCSF	Side effects	αvβ integrins	Clinical trial	Activation of dendritic cells.	Replication only in tumour cells	Human
Protein targeting	Ad-Rybp	Resistance in some cell lines, combination with other agents required.	Transformed cells	Preclinical	Introduced into normal cells, Rybp remains in the cytoplasm, whereas it remains in the nucleus of transformed cells.	Induction apoptosis	Cell culture
Viriotherapy	Telomelysin	No clearance of the tumour.	Cells expressing hTERT	Preclinical	Unknown	Tumour-targeted oncolysis.	Nude mice
	OAT	Resistance, large quantities	Cells expressing TERT	Preclinical	Unknown	Apoptosis selectively to tumour cells.	Nude mice
	CRAd5.TRAIL/siEag 1	No clearance of the tumour	Eag1-positive cancer cells	Preclinical	Silence Eag1 expression and increase sensitivity of OS cells to CRAd5.TRAIL-mediated apoptosis.	Tumour growth inhibition; Apoptosis in osteosarcoma xenografts.	Nude mice

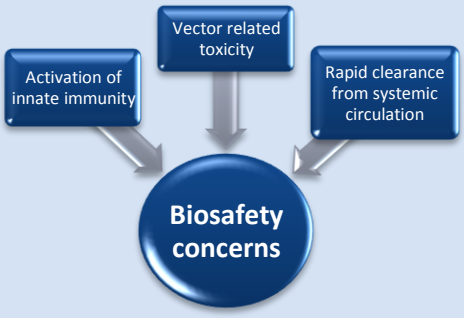
***Table 1**. A summarized view of the aspects in which adenoviral gene therapy for osteosarcoma has evolved.*

Results in clinical trials

Pesonen, S., *et al.* developed Ad5-D24-RGD-GMCSF, the first armed integrin targeted adenovirus used in humans. Summarized results can be found in the table below.

Adenoviruses used in humans	
Side effects	Fatigue, fever and injection site pain.
Virus presence in the circulation	77% of evaluable patients showed virus in circulation for at least 2 weeks.
Tumour-specific immune response	Only one patient showed induction of surviving specific T-cell 1 month after treatment with Ad5-RGD-D24-GMCSF and they were detectable also two months after virus injection.
Antitumour responses and survival	In 3/6 evaluable patients, disease previously progressing stabilized after a single treatment with Ad5-RGD-D24-GMCSF. In addition, 2/3 patients had stabilization or reduction in tumour marker levels. All patients treated with Ad5-D24-RGD showed disease progression in radiological analysis.

***Table 2.** Results obtained in human clinical trial. Data taken from (Pesonen et al., 2012).*



Conclusions

❖ Prolonging the survival of patients is a goal trying to be reached.

❖ A wide knowledge in molecular basis of osteosarcoma is essential to find new targets to reach those malignant tumour cells.

❖ An appealing aspect for future studies is the development of studies in humans. Further optimization of the treatment protocol is required, focusing on repeated injections, combining with other therapies and to lower tumour load patients, whose tumours might be less immune suppressive.

References

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