FONDAZIONE Buzzi Unicem ONLUS

MESOTELIOMA PLEURICO

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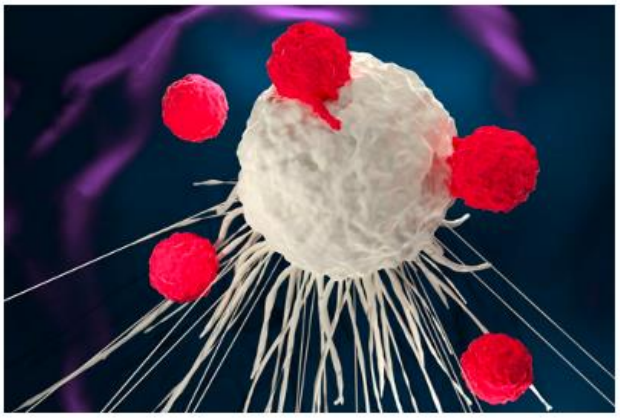
Nuove strategie terapeutiche per il Mesotelioma Pleurico Maligno: le cellule CAR T

Introduzione

Come è noto, il mesotelioma pleurico maligno (MPM) è una neoplasia aggressiva, che non è molto responsiva al trattamento standard oggi attivo in pratica clinica e che mantiene una prognosi infausta.
Tuttavia, nuovi approcci immunoterapeutici sono attualmente in fase di sperimentazione e, in particolare, vi sono dei dati relativi alla possibilità di disegnare terapie mirate a target specifici. Uno di questi è l'antigene associato al tumore mesotelina.

In questo contesto si stanno sviluppando nuove strategie terapeutiche quali la possibilità di utilizzare cellule CAR T disegnate in laboratorio, in modo che abbiano come bersaglio la mesotelina.
La seguente revisione bibliografia mira a raccogliere i dati di letteratura relativi all'applicazione dell'approccio terapeutico con CAR T al mesotelioma pleurico maligno, considerando tale strategia di trattamento come una prospettiva futura per migliorare la prognosi e gli outcomes dei pazienti affetti da tale neoplasia.
Si cercherà, dunque, di dare alcune risposte a semplici domande che il lettore potrebbe porsi nell'affrontare questi argomenti complessi, ma volti all'innovazione terapeutica nell'ambito del Mesotelioma Pleurico Maligno.



Dal Web Illustrazione: CAR-T aggrediscono una cellula cancerosa

Mesotelina

La **mesotelina** (MSLN) è stata scoperta nel 1992 nel tentativo di trovare nuovi bersagli di superficie per l'immunoterapia, tramite l'applicazione di anticorpi monoclonali.
È **espressa** a bassi livelli nelle cellule mesoteliali sane della pleura, del pericardio e del peritoneo, mentre idealmente ogni tessuto neoplasitoc di MPM potrebbe mostrare una significativa espressione di MSLN.
Il **ruolo fisiologico** della MSLN nei tessuti sani non è attualmente completamente chiarito. La MSLN è inizialmente espressa come una proteina di 71 kDa, che viene poi scissa dalla furina, provocando il rilascio di una proteina di 31 kDa, chiamata fattore potenziante dei megacariociti (MPF), mentre il frammento rimanente di 40 kDa rimane legato alla membrana cellulare attraverso un'ancora glicosilfosfatidilinositolo (GPI).

Maturazione della mesotelina (MSLN)

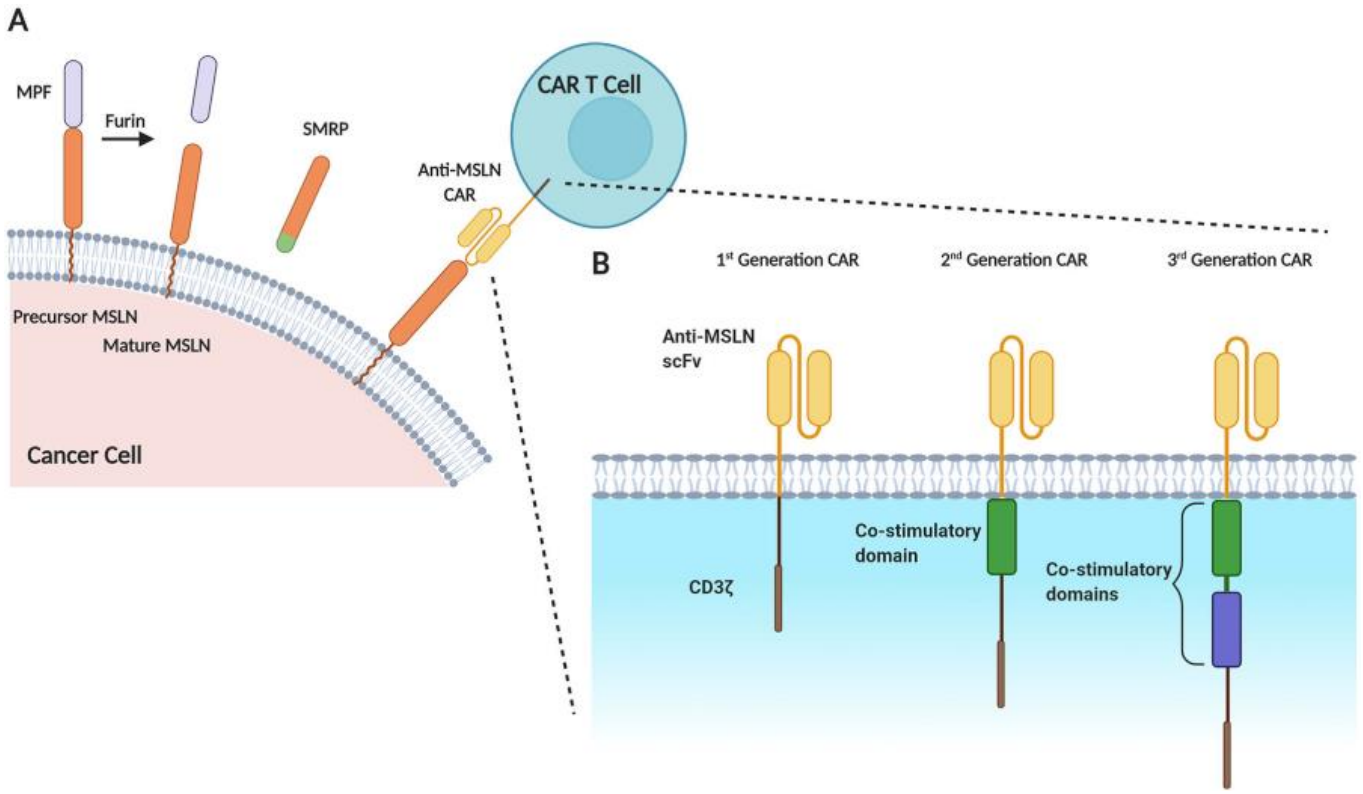


Immagine tratta dall'articolo di Castelletti et al. Biomarker Research (2021)

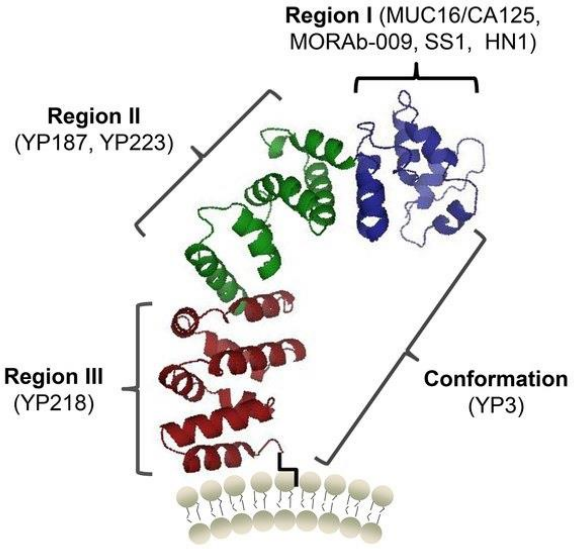
La MSLN di superficie può anche essere rilasciata creando peptide solubile legato alla mesotelina (SMRP) che può anche essere rilevato nel sangue dei pazienti con MPM.
La **MSLN** è stata al centro della ricerca sull'**immunoterapia** fin dalla sua scoperta.
Le caratteristiche che rendono MSLN un ideale bersaglio immunoterapeutico nel MPM sono molteplici, ma possono essere riassunte come segue:

- l'alto livello di espressione di MSLN nel tessuto tumorale e una bassa o nulla espressione nei tessuti sani, riducendo così le possibili tossicità;
- l'85-90% dei casi nel sottotipo epitelioide di MPM presentano un'alta espressione di MSLN [12];
- la sua espressione ad alti livelli è stata associata a una maggiore aggressività e invasività.

La **MSLN** è **costituita** come segue.
Il dominio extracellulare di MSLN comprende tre elementi contigui:

1. la regione I (residui 296-390),
2. la regione II (391-486),
3. la regione III (487-598).

La regione I è la parte distale della membrana e può legarsi alla mucina MUC16 (nota anche come CA125), che è anche espressa dalla maggior parte delle cellule MPM ed è associata alle caratteristiche di aggressività neoplastica. Questa interazione MSLN-MUC16 si dimostrata di grande importanza per l'adesione e la metastastatizzazione delle cellule tumorali ed è il bersaglio principale delle attuali immunoterapie, compresa la terapia con cellule CAR T.



Un modello di struttura proteica della mesotelina umana

Cellule CAR T

Cosa sono le terapie cellulari?

La terapia cellulare si basa sull'impiego di cellule ematologiche (ottenute dal sangue) e modificate geneticamente in laboratorio, attraverso specifiche metodiche dell'ingegneria molecolare. Per procedere con questi approcci genetici, sono necessarie strumentazioni molto complesse e laboratori dedicati ed attrezzati. Le cellule, opportunamente ingegnerizzate, possono essere iniettate nell'organismo malato, dove potranno svolgere l'attività terapeutica desiderata e programmata.

Cosa significa CAR?

CAR è una sigla che viene utilizzata per indicare i recettori chimerici dell'antigene, definiti anche immunorecettori chimerici o recettori chimerici delle cellule T o recettori delle cellule T artificiali. In pratica, si tratta di proteine recettoriali, progettate per dare ai linfociti T la nuova capacità di individuare uno specifico bersaglio proteico. I recettori sono definiti "chimerici", perché combinano in un recettore unico sia le funzioni di legame dell'antigene sia quelle di attivazione dei linfociti T.

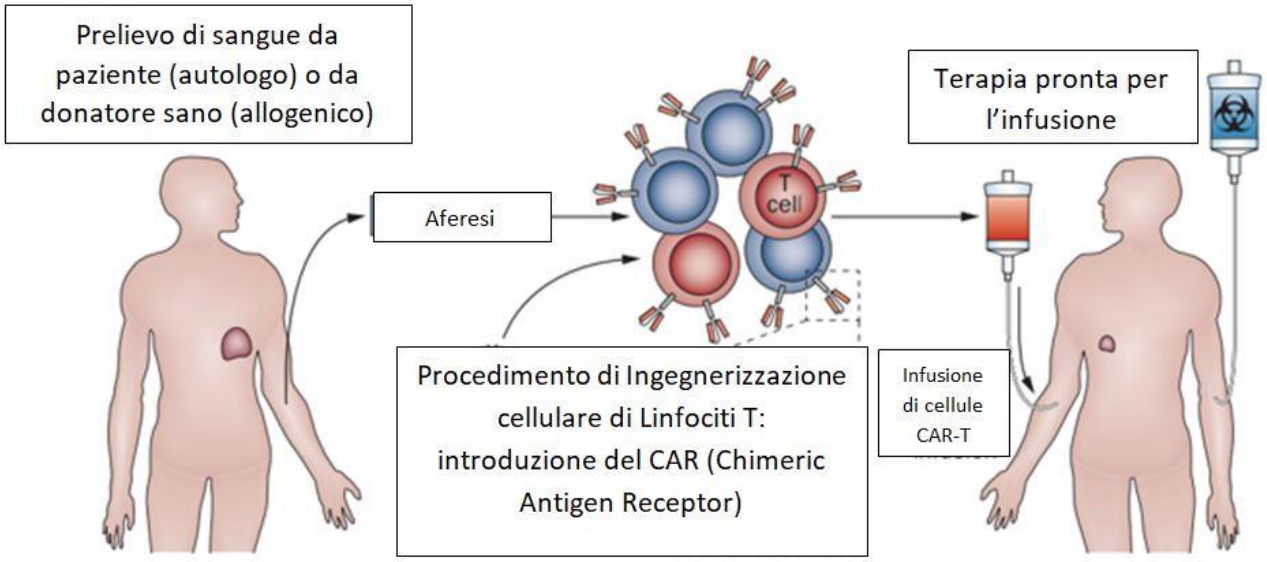
Cosa sono le CAR-T?

Le **cellule CAR T**, dunque, sono cellule del recettore chimerico dell'antigene e sono linfociti T modificati geneticamente. Lo scopo principale dell'ingegnerizzazione di tali cellule è quello di produrre un recettore delle cellule T artificiale, che viene applicato nella terapia di alcune neoplasie ematologiche. Si tratta, dunque, di un esempio convincente dell'efficacia clinica delle terapie cellulari, che producono CAR-T "educate geneticamente" a cercare, riconoscere e eliminare le cellule neoplastiche.

Come si producono le CAR-T?

La produzione di CAR-T è estremamente complessa.
Inizialmente, venie effettuato un prelievo di sangue del paziente che viene trattato laboristicamente per suddividere il materiale cellulato (le cellule sanguigne) dal plasma, tramite una tecnica definita aferesi. Tale procedimento consente di raccogliere ed isolare i linfociti del paziente. Tali cellule vengono poi inviate a laboratorio specializzati nell'ingegnerizzazione seguendo ben definiti protocolli scientifici.

Dopo aver isolato le cellule T, viene introdotto il recettore CAR (Chimeric Antigen Receptor), che è in grado di riconoscere le cellule tumorali. Infatti, tali linfociti T, definiti a questo punto CAR-T, esprimono un recettore superficiale che individua antigeni specifici espressi dalle cellule neoplastiche.



In cosa consiste la terapia con CAR-T?

In generale si può affermare che la **terapia con le CAR-T** sfrutta le cellule T ingegnerizzate con CAR l'approccio terapeutico di alcune neoplasie. Il razionale di questa applicazione terapica è la capacità delle cellule CAR T di modificare le cellule T in modo che siano in grado di riconoscere il tumore e, quindi, attaccarlo e combatterlo nella maniera più efficace possibile.
Tale trattamento viene portato a termine partendo dal sangue del paziente, che viene prelevato e lavorato in laboratorio, portando all'estrazione delle cellule T. Tali cellule, dopo essere state adeguatamente isolate, vengono quindi trattate utilizzando un vettore, che solitamente consiste in un lentivirus modificato, per fare in modo che siano in grado di esprimere uno definito CAR che le indirizzi verso un antigene tumorale specifico. E' fondamentale che le cellule CAR T siano progettate come specifiche per antigeni tipici delle cellule neoplastiche e meno presenti sui tessuti sani, per designare così un trattamento che sia il più efficace, ma anche il meno tossico possibile.
Dopo tale trattamento, le cellule così modificate possono essere reinfuse nei pazienti affetti da neoplasie. In particolare, le cellule CAR T possono essere definite:

- autologhe, se derivano dalle cellule T del paziente,
- allogeniche, se derivano da un donatore sano.

Le **CAR-T distruggono le cellule neoplastiche** attraverso diversi meccanismi, tra questi sono in grado di aumentare il grado di tossicità (citotossicità), possono costituire all'incremento della secrezione di fattori che influenzano citochine, interleuchine e fattori di crescita. Proprio per questa loro azione, tra gli effetti collaterali dell'applicazione terapeutica delle CAR-T, vi è la cosiddetta "tempesta di citochine", che può creare gravi danni, legati all'attivazione citochinica e ad altri fattori quali per esempio il volume tumorale e lo stato fisiopatologico specifico del paziente. Tale reazione avversa avviene solitamente nei primi giorni dopo la somministrazione terapeutica ed è spesso trattata con corticosteroidi e inibitori di IL6 (tocilizumab).

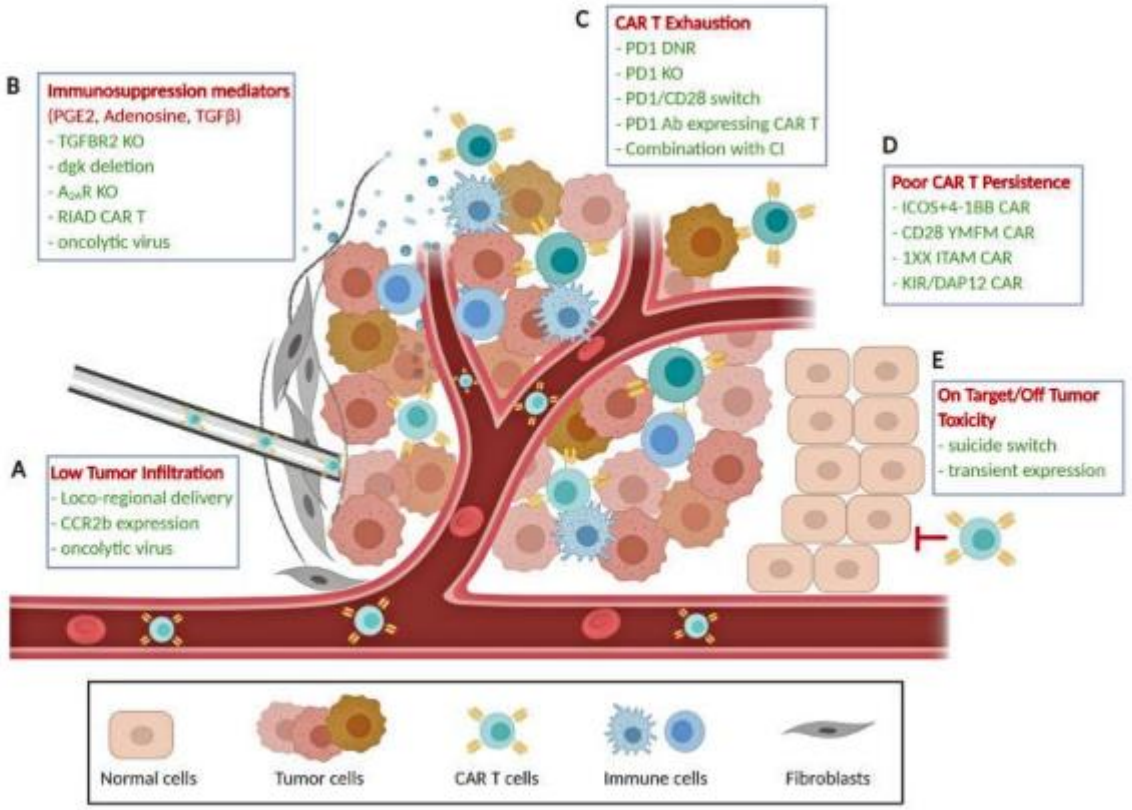


Immagine tratta dall'articolo di Castelletti et al. Biomarker Research (2021)

Terapia con CAR-T e Mesotelioma Pleurico Maligno

Le cellule CAR-T utilizzate contro il mesotelioma pleurico maligno, sono linfociti T ingegnerizzati per avere come bersaglio la mesotelina.
Come è noto, la terapia con cellule CAR-T è efficace nelle patologie neoplastiche ematologiche e le applicazioni ad oggi note per i tumori solidi sono limitate.
Nel 2019, al congresso dell'American Association fort Cancer Research (Aacr), alcuni scienziati avevano mostrato risultati incoraggianti contro questo tipo di tumore toracico, prendendo di mira la mesotelina ed utilizzando CAR-T specifiche per questo bersaglio.
I primi risultati di uno studio (trial) di fase I sono stati presentati nel marzo 2019 al meeting annuale dell'American Association Cancer Research (Abstract CT036) e poi ancora sul Journal dell'American Society of Clinical Oncology (ASCO – Abstract 2511).

In modo riassuntivo questi erano i risultati di questo studio preliminare: sono stati trattati 21 pazienti con malattia pleurica maligna (19 MPM, 1 cancro ai polmoni, 1 cancro al seno) (il 40% aveva ricevuto ≥3 linee di terapia precedente). 18 pazienti hanno ricevuto il precondizionamento con ciclofosfamide, la prima coorte non ha ricevuto ciclofosfamide. A 12 pazienti sono state somministrate cellule T CAR utilizzando una procedura di radiologia interventistica. Un paziente ha avuto neutropenia febbrile di grado 3 legata alla ciclofosfamide, mentre non sono state osservate tossicità legate alle cellule CAR T superiori al grado 2. L'ultima coorte di pazienti è stata ricoverata 2 settimane dopo l'infusione con una temperatura di >38 ° C e affaticamento. L'intenso monitoraggio della tossicità, effettuata tramite valutazione clinica (dolore toracico o addominale), radiologica (CT/PET o ecocardiogramma per versamento pericardico, ascite), laboratoristica (aumento della

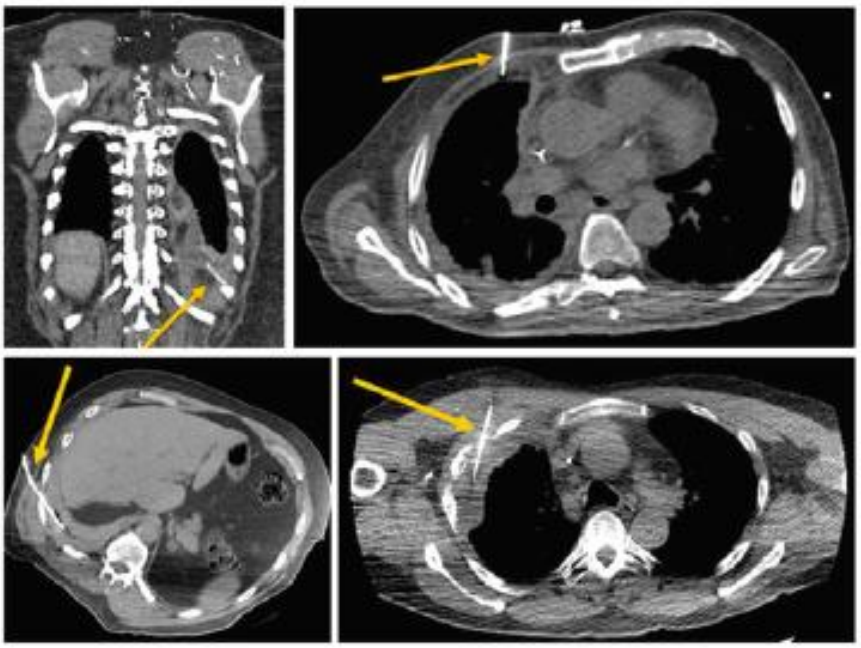
troponina) e di altro tipo (elettrocardiogramma), non ha documentato alcuna tossicità. Un paziente è stato sottoposto con successo a resezione chirurgica a scopo curativo 6 settimane dopo l'infusione di cellule T CAR. Le cellule T CAR sono state rilevate nel sangue periferico di 13 pazienti (dal 1° giorno alla 38° settimana). La persistenza delle cellule T era associata alla diminuzione dei livelli sierici di serial serum soluble MSLN-related peptide (>50% rispetto al pretrattamento) e all'evidenza della regressione del tumore negli studi di imaging. Una volta stabilita la mancanza di tossicità (6-17 settimane dopo l'infusione delle cellule T CAR), 14 pazienti sono stati trattati con immunoterapia ed hanno ricevuto agenti di blocco del checkpoint anti-PD1 (1-21 cicli) senza tossicità. La migliore risposta tra i 19 pazienti MPM (13 pazienti hanno ricevuto un agente anti-PD1; PD-L1 <10% in tutti tranne 1) è stata ottenuta da 2 pazienti che hanno avuto una risposta metabolica completa alla PET (60 e 32 settimane in corso); 5 con risposta parziale e 4 con malattia stabile.

Qualche mese più tardi, al congresso europeo di oncologia medica (ESMO – Barcellona), vengono proposti i primi risultati di uno studio di fase I che ha utilizzato le cellule CAR-T in tre pazienti affetti da mesotelioma pleurico maligno. Si trattava di uno studio limitato a pochissimi pazienti, infatti, condotto su appena tre malati di mesotelioma pleurico maligno, ma che segnava una nuova possibile strada da percorrere contro questa malattia.

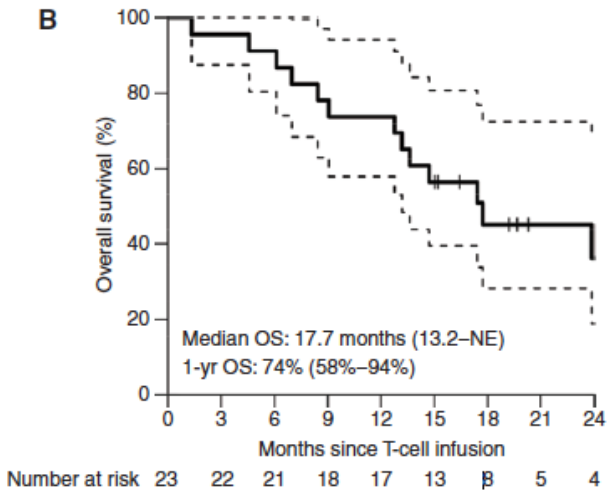
Alessandra Curioni Fontecredo, ricercatrice italiana, responsabile del Gruppo Tumori Toracici presso il Dipartimento di Oncologia ed Ematologia all'ospedale universitario di Zurigo racconta la ricerca in merito ed in una intervista commenta il suo studio dicendo: "...abbiamo somministrato le CAR-T, sviluppate in collaborazione con l'Università di Zurigo, a tre pazienti con mesotelioma pleurico, all'interno di uno studio di fase I. Il recettore chimerico utilizzato, "montato" sui linoficiti T e in grado di riconoscere le cellule tumorali, prende di mira una molecola nota coma FAP, acronimo di fibroblast activating protein: questa molecola è espressa in molti tumori epiteliali, come quelli del colon o dell'ovaio, ed è molto presente in particolare nei mesoteliomi: si trova in circa l'80% dei casi. L'idea di partire proprio dai mesoteliomi è che in questo caso i ricercatori possono procedere con una terapia locale, con iniezione delle cellule CAR-T direttamente a livello della cavità toracica. Non possiamo dir nulla circa l'efficacia della terapia, anche perché i pazienti inclusi nello studio sono stati sottoposti a chemioterapia prima e dopo la somministrazione delle CAR-T, ma dal punto di vista della sicurezza non abbiamo riscontrato effetti collaterali gravi né tossicità collegate alle cellule infuse. Dei tre pazienti trattati, uno è vivo a un anno dal trattamento e un altro a due anni. Al momento questo studio, il primo in Europa sui tumori solidi, è stato interrotto, ma stiamo lavorando per ottimizzare il recettore chimerico, per esempio tramite l'aggiunta di altre molecole di stimolazione e speriamo di avviare una nuova sperimentazione il prossimo anno".

Da questi spunti si è aperto un nuovo panorama terapeutico per il mesotelioma pleurico maligno e diversi studi sono stati proposti in ambito scientifico, per cercare di confermare questi dati e di approfondire tali scoperte. Qualora il lettore fosse interessato, si rimanda alla bibliografia indicata al termine di tale revisione.

In questa revisione bibliografica ci piace riportare in particolare una delle ultime ricerche a riguardo.
Si tratta di uno studio pubblicato a Luglio del 2021, quindi recente, su una rivista scientifica prestigiosa.
In questa ricerca, è stata testata la terapia con CAR-T che avevano come bersaglio la mesotelina. In pratica, è stata effettuata una somministrazione intrapleurale di 0,3M a 60M di cellule T CAR/kg in 27 pazienti totali, tra i quali vi erano 25 malati di MPM.

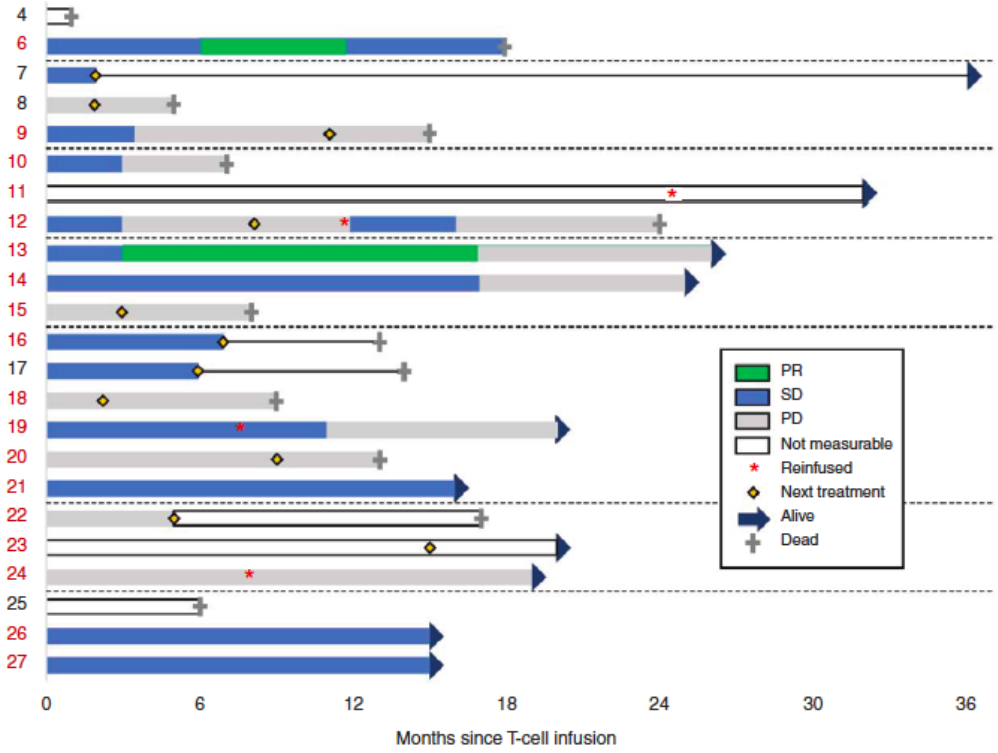


La somministrazione avveniva iniettando la terapia attraverso un catetere pleurico già in sede, oppure mediante metodiche di radiologia interventistica.
Le cellule CAR T sono state rilevate nel sangue periferico per >100 giorni nel 39% dei pazienti.
Studi precedenti avevano documentato la possibilità di associare la terapia con CAR-T all'immunoterapia, già nota ed ampiamente applicata alle neoplasie toraciche. Più nel dettaglio, tali studi sperimentali, effettuati su topi, avevano dimostrato che il blocco PD-1 migliora la funzione delle cellule CAR T nei topi. Partendo da questi dati preliminari, è stato disegnato uno studio sull'uomo di associare alla terapia con CAR-T il pembrolizumab (anticorpo monoclonale immunoterapico). Tale sperimentazione è avvenuta su 18 pazienti con mesotelioma: tra questi pazienti, la sopravvivenza globale mediana dall'infusione delle cellule CAR T è stata di 23,9 mesi (sopravvivenza globale a 1 anno, 83%).



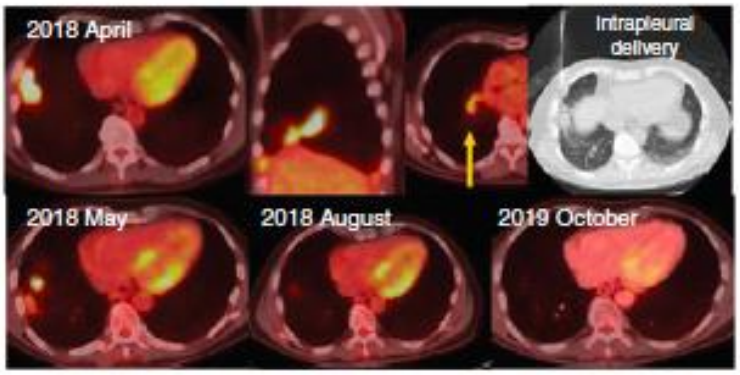
Il grafico rappresenta la sopravvivenza dei pazienti con mesotelioma pleurico maligno trattati in questo studio.
La malattia stabile è stata sostenuta per ≥ 6 mesi in 8 pazienti; 2 hanno mostrato una risposta metabolica

completa sulla PET. Pertanto, gli studiosi hanno sottolineato in questo studio come i dati supportano lo studio dell'immunoterapia combinata con cellule T CAR e agenti bloccanti PD-1 nei tumori solidi.



Il grafico rappresenta gli outcomes dai pazienti affetti da MPM trattati in questo studio
(PR = Partial Response, SD = Stable Disease, PD = Progression Disease.)

Le fotografie seguenti dimostrano esempi pratici di risposta al trattamento in pazienti con mesotelioma.



I ricercatori hanno concluso che la somministrazione locale della terapia con cellule T CAR mirata alla mesotelina e seguita dalla somministrazione di pembrolizumab è fattibile, sicura e dimostra evidenza di efficacia antitumorale in pazienti con malattie maligne della pleura.

Conclusioni

Lo studio delle cellule CAR T ha permesso di analizzare la loro applicazione non solo per le malattie ematologiche, ma anche per i tumori solidi.
Tra questi, il mesotelioma pleurico maligno, è diventato potenziale bersaglio di tali trattamenti.
Specifiche cellule del sistema immunitario opportunamente ingegnerizzate, diventano efficaci contro target specifici e se questi bersagli si trovano sulle cellule neoplastiche del mesotelioma pleurico maligno, ecco che è possibile disegnare strategie terapeutiche ben definite.
Un nuovo approccio terapeutico in questo panorama di innovazione per il mesotelioma pleurico maligno è rappresentato dall'applicazione delle cellule CAR T e risultati preliminari a questo proposito mostrano interessanti risvolti traslazionali ed offrono prospettive future incoraggianti.
Ulteriori studi dedicati potranno confermare tali ricerche e portare eventualmente in pratica clinica nuove terapie per questa patologia pleurica.

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