



ORAL PRESENTATION

Open Access

Cytokine Induced Killer cells effectively kill chemo-resistant melanoma cancer stem cells

Loretta Gammaitoni¹, Lidia Giraud^{1,2*}, Valeria Leuci¹, Giulia Mesiano¹, Michela Cangemi², Alessandro Zaccagna¹, Alberto Pisacane¹, Susanna Gallo², Fabrizio Carnevale-Schianca¹, Massimo Aglietta^{1,2}, Dario Sangiolo^{1,2}

From Melanoma Bridge Meeting 2014
Naples, Italy. 03-06 December 2014

Background

Metastatic Melanoma (mMel) is considered refractory to conventional chemotherapies. New molecular targeted approaches, inhibiting mutated forms of the serine-threonine kinase B-RAF, significantly increased the response rate but patients almost invariably relapse and prognosis remains severe [1,2]. Open challenge is the characterization and targeting of cancer stem cells (CSCs), considered responsible for chemoresistance and disease relapse. Adoptive immunotherapy holds great promises for the treatment of mMel and research efforts are ongoing to explore its potential activity against melanoma CSCs (mCSCs). Cytokine Induced Killer (CIK) cells are a subset of *ex vivo* expanded T lymphocytes with mixed CD3⁺CD56⁺ phenotype and endowed with HLA-unrestricted tumor killing activity. We and others recently reported the preclinical activity of CIK cells against several solid tumors including mMel [3].

Aim of our research is to explore the preclinical activity of CIK cells against autologous mCSCs surviving treatments with chemo or molecular targeted therapies.

Material and methods

We set a preclinical autologous immunotherapy model with primary melanoma cultures and CIK cells generated from patients treated at our Center. To visualize mCSCs we transduced tumor cells with a lentiviral CSC-detector vector encoding enhanced Green Fluorescent Protein (eGFP) under control of the stem-gene oct4 promoter. We treated all mMel cultures with chemotherapy drug fotemustine (IC50 dose). Melanoma cultures harboring BRAF V600E mutations were also treated with BRAF inhibitor (BRAFi) dabrafenib (IC50 dose). We evaluated

the presence of residual mCSCs among mMel cells surviving 72h of treatment and explored their susceptibility to immunotherapy with autologous CIK cells.

Results

We visualized mCSCs within 11 mMel cultures (3/11 BRAF V600E mutated); median value of eGFP+mCSCs was 15% (range 3.5-26.4%). Putative mCSCs displayed a relative resistance to conventional treatments. The presence of eGFP+mCSCs increased of 39% and 25% among melanoma cells that survived exposure to fotemustine and BRAFi respectively, compared to untreated controls (n=11). CIK cells effectively killed autologous mMel and mCSCs. Tumor specific killing, equally involving bulk mMel targets and mCSCs, ranged between 75% and 33% at effector target ratios of 40:1 and 1:1 respectively (n=8).

Conclusion

We provided first proof of concept that putative mCSCs are relatively resistant to conventional treatments with chemo or molecular targeted therapy and susceptible to immunotherapy killing by autologous CIK cells. These preclinical findings support the hypothesis that mCSC may be responsible for disease relapses and support designing of experimental immunotherapy clinical trials with CIK cells in mMel settings.

Authors' details

¹Candiolo Cancer Institute – IRCCS, Candiolo, Italy. ²University of Torino, Department of Oncology, Turin, Italy.

Published: 15 January 2015

References

1. Chapman PB, Hauschild A, Robert C, Haanen JB, Ascierto P, Larkin J, Dummer R, Garbe C, Testori A, Maio M, Hogg D, Lorigan P, Lebbe C,

¹Candiolo Cancer Institute – IRCCS, Candiolo, Italy
Full list of author information is available at the end of the article

Jouary T, Schadendorf D, Ribas A, O'Day SJ, Sosman JA, Kirkwood JM, Eggermont AM, Dreno B, Nolop K, Li J, Nelson B, Hou J, Lee RJ, Flaherty KT, McArthur GA, BRIM-3 Study Group: **Improved survival with vemurafenib in melanoma with BRAF V600E mutation.** *N Engl J Med* 2011, **364**(26):2507-2516.

2. Flaherty KT, Infante JR, Daud A, Gonzalez R, Kefford RF, Sosman J, Hamid O, Schuchter L, Cebon J, Ibrahim N, Kudchadkar R, Burris HA 3rd, Falchook G, Algazi A, Lewis K, Long GV, Puzanov I, Lebowitz P, Singh A, Little S, Sun P, Allred A, Ouellet D, Kim KB, Patel K, Weber J: **Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations.** *N Engl J Med* 2012, **367**(18):1694-1703.
3. Gammitoni L, Giraudo L, Leuci V, Todorovic M, Mesiano G, Picciotto F, Pisacane A, Zaccagna A, Volpe MG, Gallo S, Caravelli D, Giaccone E, Venesio T, Balsamo A, Pignochino Y, Grignani G, Carnevale-Schianca F, Aglietta M, Sangiolo D: **Effective activity of cytokine-induced killer cells against autologous metastatic melanoma including cells with stemness features.** *Clin Cancer Res* 2013, **19**(16):4347-4358.

doi:10.1186/1479-5876-13-S1-O1

Cite this article as: Gammitoni *et al.*: Cytokine Induced Killer cells effectively kill chemo-resistant melanoma cancer stem cells. *Journal of Translational Medicine* 2015 **13**(Suppl 1):O1.

**Submit your next manuscript to BioMed Central
and take full advantage of:**

- Convenient online submission
- Thorough peer review
- No space constraints or color figure charges
- Immediate publication on acceptance
- Inclusion in PubMed, CAS, Scopus and Google Scholar
- Research which is freely available for redistribution

Submit your manuscript at
www.biomedcentral.com/submit

