OncoImmunology 1:2, 232–233; March/April 2012; © 2012 Landes Bioscience

Cancer immunotherapy
Benefit and harm?

Dainius Characiejus

Faculty of Medicine; Vilnius University; Vilnius, Lithuania

Keywords: cancer, immunotherapy, prediction, survival, CD8, CD57

Abbreviations: RCC, renal cell carcinoma; IFNα, interferon-α

In this article, evidence is reviewed suggesting that the outcome of cancer immunotherapy depends on pre-treatment immune parameters of a patient. The results described in the article show that immunotherapy may prolong survival in certain subgroups of cancer patients, while in other subgroups a cancer-promoting effect of this treatment modality cannot be excluded.

Cancer immunotherapy is a rapidly expanding area of research and clinical practice. Cytokines, monoclonal antibodies, vaccines and adoptive cell immunotherapy are increasingly being studied in trials and used in clinics. There is one aspect, however, which has been largely ignored in cancer immunotherapy studies: heterogeneity of survival rates among untreated patients. If this is taken into account, two questions remain to be answered. First, what is the role of immunological factors in determining the survival of untreated cancer patients? Second, do patients with good immunological prognostic factors benefit from immunotherapy?

Regarding the clinical outcome, renal cell carcinoma (RCC) is one of the most heterogeneous of adult malignancies. In general, outcome of patients with metastatic RCC is poor with the median survival of approximately 1 y. However, some primary tumors and metastases of RCC, especially pulmonary parenchymal lesions, may have periods with little or no growth during many months.[1] A subset (from 10% to 20%) of patients with metastatic RCC survive 5 or more years.[1,2]

In the late nineties, our group has studied the prognostic significance of peripheral blood lymphocyte subsets in advanced RCC patients using flow cytometry. We found remarkable differences in overall survival of advanced RCC patients based on peripheral blood levels of $CD8^{high}CD57^{+}$ lymphocytes.[3] In our analysis, the median overall survival of patients with $<$ 30% $CD8^{high}CD57^{+}$ lymphocytes in the $CD8^{+}$ subset was 23.5 mo (the "relatively good prognosis group"), whereas the median overall survival of patients with $\geq$ 30% $CD8^{high}CD57^{+}$ lymphocytes in the $CD8^{+}$ subset was only 6 mo (the "bad prognosis group"). High expression of CD8 antigen distinguishes $CD8^{+}$ T cells from $CD8^{+}$ NK cells that have low expression of CD8.[4] Expression of CD57 antigen on T lymphocytes is regarded as a marker of immune deficiency in patients with autoimmune disease, infectious diseases and cancer.[5] Thus, differences in survival among untreated advanced RCC patients may depend on immunological factors, i.e., levels of $CD8^{high}CD57^{+}$ lymphocytes.

During 1995–1999, interferon-α (IFNα) was just being introduced in Lithuania, and no strict guidelines toward its use for treatment of metastatic RCC were available. Due to considerable variability in approach to treatment of metastatic RCC patients in Lithuania, we were able to select subgroups of patients treated and non-treated with IFNα. Thus, we had the opportunity to perform a retrospective analysis of the predictive significance of peripheral blood lymphocyte subsets for treatment with IFNα of patients with advanced RCC. Treatment with IFNα significantly increased the median overall survival of the "bad prognosis group" RCC patients (from 6 to 18.5 mo). In contrast, a trend toward decreased median overall survival was observed in the "relatively good prognosis group" after treatment with IFNα (13.6 mo of IFNα-treated patients vs. 23.5 mo of patients non-treated with IFNα).[3] These our results suggest, that immunotherapy with IFNα may benefit patients with poor immunological prognostic factors, whereas this treatment may even be harmful for patients with good immunological prognostic factors.

Thousands of melanoma patients have been enrolled in adjuvant IFNα trials with the aim to determine a statistically significant improvement in survival. In a recent systematic review and meta-analysis of 14 randomized controlled trials including a total of 8,122 patients, it was shown that treatment with IFNα statistically significantly improves the overall survival of high-risk melanoma patients with a risk reduction of 11%.[6] However, it has to be taken into account that 60% of patients

Correspondence to: Dainius Characiejus; Email: dainius.characiejus@gmail.com
Submitted: 09/14/11; Revised: 09/22/11; Accepted: 09/22/11
http://dx.doi.org/10.4161/onci.1.2.18183

with stages II-III cutaneous melanoma survive 5 y without any treatment.[6] Can these patients benefit from adjuvant IFNα therapy?

Several published reports show that longer survival of melanoma patients is associated with increased levels of $CD8^+$ $CD57^+$ T lymphocytes in peripheral blood (for a review see ref. 7). However, to our knowledge, $CD8^+CD57^+$ T lymphocyte levels have never been measured in trials of adjuvant IFNα in high-risk melanoma. Our results have shown that pre-treatment levels of peripheral blood $CD8^{high}CD57^+$ lymphocytes remarkably predict the survival of high-risk melanoma patients after treatment with IFNα. Median overall survival of patients with $<$ 23% $CD8^{high}CD57^+$ lymphocytes in the $CD8^+$ subset was not reached at a median follow-up of 24.6 mo, whereas median overall survival of patients with $>$ 23% $CD8^{high}CD57^+$ lymphocytes was only 14.2 mo.[8] The detrimental effect of adjuvant IFNα in the latter group of patients cannot be excluded.

In conclusion, our results reviewed in this article and the results by other authors (for a review see ref. 9) strongly suggest that the outcome of immunotherapy depends on pre-treatment immune parameters of a cancer patient. Immunotherapy may prolong survival in certain subgroups of patients, most likely in those with poor immunological prognostic factors. However, immunotherapy should be administered cautiously to patients with good immunological prognostic factors, because a cancer-promoting effect of this treatment modality cannot be excluded (for a review see ref. 7). Schematic outline of the implications of the data reviewed in this article is shown in **Figure 1**.

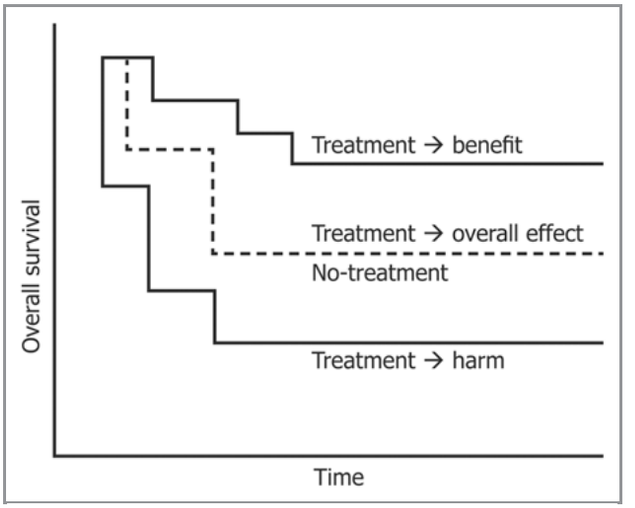

Figure 1. Schematic outline of the implications of the data reviewed in this article. Depending on pre-treatment immune parameters, immunotherapy may prolong survival in one subgroup of patients, while in another subgroup survival may be decreased compared with non-treated patients. As a result, the total effect of the therapeutic intervention may be nullified.

$CD8^+$ T lymphocytes are well-documented effectors of tumor immunity. There is ample evidence on the prognostic significance of $CD8^+$ lymphocytes within a tumor or in peripheral blood of cancer patients.[9,10] Thus, numbers and maybe functional characteristics of $CD8^+$ T lymphocytes or their subsets may reflect the immunologic reactivity of the cancer patient and predict beneficial or harmful effects of immunotherapy. Our results support the predictive significance of peripheral blood $CD8^{high}CD57^+$ lymphocyte levels, but more research is needed.

References

1. Dekernion JB, Ramming KP, Smith RB. The natural history of metastatic renal cell carcinoma: a computer analysis. J Urol 1978; 120:148-52; PMID: 78992
2. Martel CL, Lara PN. Renal cell carcinoma: current status and future directions. Crit Rev Oncol Hematol 2003; 45:177-90; PMID:12604128; http://dx.doi.org/10.1016/S1040-8428(02)00076-8
3. Characiejus D, Pašukonienė V, Kazlauskaitė N, Valuckas KP, Petraitis T, Mauricas M, et al. Predictive value of CD8highCD57+ lymphocyte subset in interferon therapy of patients with renal cell carcinoma. Anticancer Res 2002; 22:3679-83; PMID:12552976
4. Wang ECY, Moss PAH, Frodsham P, Lehner PJ, Bell JI, Borysiewicz LK. CD8highCD57+ lymphocytes in normal, healthy individuals are oligoclonal and respond to human cytomegalovirus. J Immunol 1995; 155: 5046-56; PMID:7594513
5. Focosi D, Bestagno M, Burrone O, Petrini M. CD57+ T lymphocytes and functional immune deficiency. J Leukoc Biol 2010; 87:107-16; PMID:19880576; http://dx.doi.org/10.1189/jlb.0809566
6. Mocellin S, Pasquali S, Rossi CR, Nitti D. Interferon alpha adjuvant therapy in patients with high-risk melanoma: a systematic review and meta-analysis. J Natl Cancer Inst 2010; 102:493-501; PMID: 20179267; http://dx.doi.org/10.1093/jnci/djq009
7. Characiejus D, Hodzic J, Jacobs JJL. "First do no harm" and the importance of prediction in oncology. EPMA J 2010; 1:369-75; PMID:21151487; http://dx.doi.org/10.1007/s13167-010-0042-1
8. Characiejus D, Pašukonienė V, Jonušauskaitė R, Kazlauskaitė N, Aleknavičius E, Mauricas M, et al. Peripheral blood CD8highCD57+ lymphocyte levels may predict outcome in melanoma patients treated with adjuvant interferon-alpha. Anticancer Res 2008; 28:1139-42; PMID:18505049
9. Characiejus D, Jacobs JJ, Pašukonienė V, Kazlauskaitė N, Danilevičiūtė V, Mauricas M, et al. Prediction of response in cancer immunotherapy. Anticancer Res 2011; 31:639-47; PMID:21378350
10. Characiejus D, Pašukonienė V, Jacobs JJ, Eidukevičius R, Jankevičius F, Dobrovolskienė N, et al. Prognostic significance of peripheral blood CD8highCD57+ lymphocytes in bladder carcinoma patients after intravesical IL-2. Anticancer Res 2011; 31:699-703; PMID: 21378359