A new strategy for immune manipulation of advanced solid cancers

The biological cancer hallmarks and the current model

In the updated ongoing model, genomic instability and inflammation are the basis of all the cancer hallmarks: sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, activating invasion and metastasis, reprogramming energy and metabolism and evading immune destruction. Moreover, the network which cancer growth and progression is based on can be represented as an overall integrated circuitry comprising a few interconnected subcircuits. In turn, each subcircuit comprises multiple interconnected pathological molecular pathways fostering different hallmark capabilities.

Probable reasons for the discrepancy between genetic and biological advances and clinical outcome

Likely the main reasons of the discrepancy between the biological advances in knowledge and persistently poor outcome of advanced solid cancers from therapies involve tumour, microenvironment and conventional therapies. Spatial (many genetic and epigenetic alterations that differ within the same tumour and from one to another) and temporal (any tumour can change its phenotype during progression) heterogeneities are main characteristics of cancer. The cross-talk between stroma and cancer cells is the microenvironment contribution that further increase the complexity of the overall network of the molecular pathways. Finally, "the contextual signaling" that is different extracellular signaling present in the immediate milieu account for different adaptive responses of cancer cells while toxicity and early arising of resistance account for time-limited efficacy of the conventional treatments.

Tumor burden and the immune response to cancer

Immune system failure joins with development of cancer. Larger is the tumor burden higher its immunoevasion is. Immune evasion occurs with immune suppression and immunoediting. It is likely that in condition of minimal residual disease immune evasion is downregulated as well as in advanced cancer in prolonged response to conventional therapy. We suggest that in both these conditions immunomanipulation can be more successful. Experimental and clinical findings from us and other authors support this hypothesis.

A novel strategy of advanced cancer immune manipulation

Based on this, a novel therapeutic strategy for breast and other types of solid cancers at high risk of relapse is proposed. In particular, with regard to endocrine-dependent cancers, in metastatic breast cancer patients responding or stable during endocrine therapy significantly prolonged DFS

and/or OS have been reported by combining conventional hormone therapy (HT) with new schedules of immune therapy. Therefore, these schedules could be considered in locally advanced breast cancer patients for the same duration for which anti-oestrogens are currently recommended (5-7 years). It can be inferred that by replacing conventional anti-oestrogens with anti-androgens, the same schedules of hormone immune therapies could be evaluated in metastatic and locally advanced hormone-dependent prostate cancers respectively. Following clinical results in previous studies, in patients with locally advanced endocrine non dependent cancers, in the initial 6-8 months after conventional adjuvant chemotherapy (CT) and/or radical resection, regular administration of a few cycles (3-4) of anti-proliferative drugs with concomitant immune-modulating properties, such as taxanes or anti-metabolites (5FU, capecitabine),at low doses every 8-12 months for a few years with or without partially synergizing immune drugs can be considered.

Cancer type	Target population	Therapy		Aim
		Conventional	Immunotherapy	
Breast and prostate	*Endocrine-dependent	Hormone therapy	IL-2-IFN-beta sequence	Significant delay of recurrence Significant decrease of recurrence rate
Breast, prostate and other solid tumors	Non-endocrine-dependent	**few cycles of taxanes, gemcitabine, carboplatin, vinorelbine, antimetabolites (5-FU, capecitabine) at low dose regularly given every 8-12 monts for 5 years	With or without inhibiting immune suppression therapy according to the cancer phenotype	Significant delay of recurrence Significant decrease of recurrence rate Delay of metastatic progression

Tab. 1. Proposal of immunotherapy for advanced solid cancers with minimal residual disease (MRD)
*In prostate cancers, anti-androgens replace anti-estrogens; **antiblastics should be chosen consistent with cancer type and current therapeutic recommendations; also see text.

The main aim of this additional adjuvant CT is to gradually switch off the mechanisms triggering the proliferation of residual resistant cancer cells and the concomitant immune evasion. In cases of resistant/non-endocrine-dependent breast and other types of solid cancers in clinical benefit (CR+PR+SD) following conventional therapy, immune maintenance therapy (immunomodulatory/stimulating drugs) can be attempted to delay the re-growth of tumour. In these cases, provided that immune tolerance is directly correlated with tumor burden, more therapeutic efficacy is expected when immune manipulation follows CR or PR rather than SD. Table 1 summarizes these proposals. We are moving on with this strategy in breast, prostate and gastro-intestinal cancers.

Andrea Nicolini [1], ***Paola Ferrari*** [1], ***Giuseppe Rossi*** [2], ***Angelo Carpi*** [3]
[1]*Department of Oncology, Transplantations and New Technologies in Medicine, University of Pisa, Italy*
[2]*National Research Council (CNR), Epidemiology and Biostatistics Unit, Institute of Clinical Physiology and G. Monasterio Foundation, Pisa, Italy*
[3]*Department of Clinical and Experimental Medicine, University of Pisa, Italy*

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