Pulmonary hypertension: Another light in the dark tunnel. Learning the lesson from cancer

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Pulmonary hypertension (PH) is a fatal disease. If untreated, the median survival is 2.8 years.[1] The disease is clinically characterized by a progressive increase in pulmonary vascular resistance (PVR) secondary to continuous obliteration of pulmonary arteries by a proliferative process involving all pulmonary vascular layers.[2]

In the last PH world congress at Dana Point, the disease was classified into five groups.[3] Group 1, which is called pulmonary arterial hypertension (PAH), has gained a lot of interest during the last few years. Such interest has lead to a better understanding of the complex disease pathobiology and, subsequently, the development of many effective drugs that improve hemodynamics, exercise performance, quality of life, and survival.[4]

Different pathobiological mechanisms triggered by endothelial cells dysfunction have been clearly identified and observed in PAH. Such mechanisms include smooth muscle vasoconstriction, shear stress abnormality, pulmonary vascular wall remodeling, inflammation, and *in-situ* thrombosis.[5] Plexogenic arteriopathy, however, is the most characteristic feature of PAH, in which the pre-capillary vessels display varying degree of abnormalities involving proliferation of both the intima and media.[6]

During the last decade, significant advances have been achieved in the management of PAH. The availability of new classes of vasodilators that also modify cell proliferation and target-specific active pathobiological pathways, so-called targeted therapy, has been considered as a major breakthrough in treating this condition. The first class of medication is the prostanoid, which is a very potent vasodilator of all vascular beds and potently inhibit proliferation of pulmonary smooth muscle via a cAMP-dependent pathway.[7] The second class of targeted medication is the endothelin-1 receptor antagonists that inhibit the potent vasoconstriction and smooth-muscle mitogenic effects of endothelin-1 on pulmonary vasculature by inhibiting its effect on endothelin A and B receptors located on pulmonary smooth muscles.[8] The third class of medication is the phosphodiesterase-5 inhibitors that modulate the content of cGMP in vascular smooth muscle by preventing its degradation by phosphodiesterase-5 enzymes. This mechanism leads to augmentation of pulmonary vasodilatation and inhibit smooth muscle proliferative activities.[9] Despite their antiremodeling/antiproliferative effect, these drugs are largely considered as vasodilators and certainly more specific treatment targeting other active signaling are needed before long-term control of the disease is to be achieved.

Recent studies have shifted our understanding toward the neoplastic features of PAH by focusing on the uncontrolled proliferation of many cellular layers and the bypassing of the mitochondria-controlled apoptosis process.[2] Such imbalance between cell generation and cell termination/deaths raised the concept of "pulmonary circulation neoplasm" theory. Furthermore, the continuous cell mitogenic activities in PAH even under hypoxic conditions by utilizing anaerobic glycolysis for energy (i.e., ATP) production and the inhibition of the mitochondrial capacity to maintain the balance of cell birth: death ratio are very similar to many cancer situations.[2]

Consequent to this recent understanding, a phase III study using anti-proliferative, anti-cancer, Tyrosine Kinase inhibitor (TKIs), therapy (imatinib) in advanced PH patients showed a very impressive positive effect on the patient exercise capacity (6 minute walk test) and on the disease hemodynamics by significantly reducing the PVR and improving cardiac output.[10]

Despite this encouraging early result of TKIs and the use of anticancer therapy in PH management, an important question remains: "did we really learn the lesson from cancer?"

The following are important considerations to be learned from cancer before TKIs (or other anti-cancer therapy) can be used in treating "pulmonary circulation neoplasm".

- Recent evidence in non-small cell lung cancer (NSCLC) has provided very important insights into the molecular basis of this disease and has also revealed an important concept for targeting tyrosine kinases by rationally selected therapies toward a spectrum of genetic mutations/lesions found in NSCLC.[11] The significant variation in mutational profiles seen in NSCLC patients suggests that each tumor represents a distinct disease state that can only be effectively treated with a precise therapy that targets the specific combination of genetic changes unique to each tumor. This finding has created the concept of "personalized treatment" to each case and led to a breakthrough in management of NSCLC.[12]
- The complexity of genetic heterogeneity and pathway redundancy that characterize advanced NSCLC provide an insight about the limitations of single-agent therapies and suggests that more sophisticated chemotherapeutic regimen that target multiple pathways at the same time will be required to effectively treat this disease.

Based on these tremendous advances in understanding the genome sequencing and mutation in NSCLC and its therapeutic implications, we strongly believe that PAH treatment should probably follow the same path.

One theme is to determine the genetic alterations to key growth factor signaling pathways that regulate cell proliferation, survival, and migration before starting therapy. It is only in those patients with very specific gene mutation and active signal propagation by kinase cascades, suggesting that they would be excellent targets for rationally designed TKIs, should treatment with these agents considered.

The second theme is toward upfront combination therapy by more than one chemotherapeutic agent. This will probably help not only to overcome drug resistance mechanism, but also to address different active signaling pathways that are likely to be present in most, if not all, PAH patients.

We believe that the time has arrived toward adopting "antineoplastic therapy" in the treatment of PAH, and not simply counting on vasodilator therapy. The recent small effort toward using this approach has shown some benefit, but, in our opinion, was not optimally utilized.

Learning our lesson fully from cancer medicine should hopefully lead us to the light at the end of the dark tunnel.

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