Cancer Management: Organ Based Approach is being Blurred

Shahid Pervez[1*]

[1]*Aga Khan University Hospital, Karachi, Pakistan*

For decades cancer management has been based on organ systems like 'Breast Cancer' is to be treated differently from 'colon cancer' or 'lung cancer'. However, cancer genetics and better understanding have led to a paradigm shift in the way cancer is treated. What is now looked at is the leading carcinogenic pathway *i.e.* what is driving the growth irrespective of the fact from which organ system it originated [1].

This is now a routine practice to request predictive markers as what is termed as 'reflex testing', for instance as per the Royal College of Pathologists, UK guidelines 'mismatch repair genes (MMR) [2], K-Ras, HER2, BRAF are a standard part of patient care in large bowel cancer. Similarly, ER, PR, and HER2 for breast cancer [3] and EGFR mutational analysis, ROS-1, and ALK in non-small cell lung cancer [4].

This means that it is no truer that all breast cancer, colon cancer, or lung cancer shall be treated in a particular way as a breast cancer driving mutational pathway may be more like colon cancer than another breast cancer.

This paradigm shift, in the way cancer is looked at, diagnosed, and treated is the direct result of the genetic revolution. With the arrival of NGS, it is now a new ballgame altogether. WHO blue books on classification and diagnostic criteria of cancers are a vivid example of this revolution [5].

A major concern with conventional chemotherapeutic agents has been the severe and sometimes intolerable side effects by their mode of action is non-discriminatory. These agents kill all dividing cells leading to these life-threatening side effects. For instance, bone marrow cells divide all the time, so bone marrow suppression, hair growth, hence hair fall, gut stem cells are active in replenishing old cells, diarrhea, and so on. Bone marrow suppression and its possible consequences are particularly dreadful. In the interim period when bone marrow manages to replenish, the patient is highly vulnerable to all kinds of infections and their fallouts.

Historically it all started with Oestrogen Receptor utility in breast cancer by blocking oestrogen-driven growth with the help of drugs like Tamoxifen. Later HER2 carcinogenic pathway due to the amplification of the HER2 gene led to the development of the humanized monoclonal antibody trastuzumab (Herceptin) in the 90's. Since then, many driving mutations have been identified, and targeted therapy has become the norm with hundreds of options already in place while manyfold are under clinical trials [6].

Immune-checkpoint inhibitors were another milestone once it was realized that we do have immunity against cancer cells, however, our immune response primarily by T-cells is made ineffective by PD1 receptors on T-cells and its ligand PDL1 on tumor cells leading to inhibition of T-cells. Immune checkpoint inhibitors break this binding leading to an effective immune response against cancer cells and miraculous results in many cases. Ironically this is potentially applicable to most if not all common cancer types [7].

This has resulted in a relatively newer major role of pathologists as a predictor by running a battery of relevant tests with robust quality control utilizing techniques like 'Immunohistochemistry', 'PCR', 'in-situ hybridization', and NGS.

Finally with this shift comes the rude awakening and reality for countries that come under the category of LMIC (Low to Middle-income countries) as these drugs are prohibitively expensive and way beyond the reach of a major segment of the population. Only plausible solutions and silver-line may be provided once the patent of these drugs is over and LMIC is licensed to prepare these at industrial levels at a fraction of the cost based on generic formulas of these drugs [8].

**Corresponding author: Shahid Pervez, Aga Khan University Hospital, Karachi, Pakistan, E-mail: shahid.pervez@aku.edu*

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