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Editorial

Advances in immuno-oncology and precision oncology: Where are we heading?

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There has been a significant advance in the management of advanced malignancies in the last decade. Immunotherapy and precision therapy have significantly changed the way we manage our patients with cancer.[1] In fact, these treatments are percolating into the management of adjuvant treatment as well. The burning examples include adjuvant Osimertinib post-surgery in EGFR mutated non-small cell lung cancer (NSCLC), and adjuvant durvalumab post definitive chemo-radiation in NSCLC.[2] Besides histology, the treatment now depends on microsatellite instability (MSI) status, programmed death-ligand expression, and various other genomic alterations seen on the tumor tissue. Recent style of treatment with plasma genotyping has also proved to be beneficial for the patients with recurrent disease and where the biopsied tumor tissue is inadequate. Plasma genotyping provides the opportunity for obtaining the molecular information without the need of multiple invasive procedures. In fact, the role of cell-free DNA has been established in the management of advanced NSCLC, for patients progressing on first/second-generation EGFR tyrosine kinase inhibitors to detect T790M mutation.

These strategies have become very useful for improving the outcomes of our cancer patients. There were so many publications about two decades back discussing chemotherapy versus best supportive care alone in advanced NSCLC patients. Who would have thought about a decade back that we would be discussing 5-year survival of metastatic NSCLC (with EGFR/ALK mutations) patients? Similarly, there is now data for 10-years survival of metastatic melanoma patients treated with immunotherapy. Another example of taming the cancer is Sotorasib targeting KRASG12C mutation, entrectinib/Larotrectinib for neurotrophic tyrosine/tropomyosin receptor kinase (NTRK) mutations.[3] For a very long time, KRAS mutations were considered to be non-targetable. These targeted therapies reinforce our belief on the saying "No disease is bad or incurable, it is only our inability to know the correct way of treating that disease." Another example which we would like to provide is the treatment of acute promyelocytic leukemia, this was considered a disease with death imminent after its diagnosis with very limited benefit from treatment. However, we are all aware that now this is the type of acute myeloid leukemia with maximum chances of cure. Chronic myeloid leukemia has been now converted into any other chronic disease such as diabetes and hypertension. All these are achievements of precision oncology and immunotherapy, which we will continue to cherish and build upon them for further improvement in outcomes and quality of life of our patients.

The role of next-generation sequencing (NGS) and genomic analysis of the tumor has played a vital role in providing the personalized treatment.[4] There are constant discussions and debate

about the role of NGS in terms its actual utility in improving the outcomes. However, if you do not test, you won't know! Thus, the impetus is now on testing and knowing the genetic make-up of the tumor, which in turn, will provide useful information for its treatment. We completely agree that this field is evolving, and it will be taking some more time before we are able to find some personalized treatment for every patient with cancer. Besides, it is imperative to find more biomarkers so that we can prepare some sort of "cancer immunogram" which will help us to decide the utility (or, futility) of immunotherapy in patients with advanced cancer.[5] Overall the consolidated concept for precision oncology is to provide benefit of personalized therapy with minimal toxicity and greater efficacy. However, the labs which are doing these molecular tests should have adequate quality checks, not only internal but external as well, to ensure best possible standards in terms of quality of the testing and reporting.

The past decade has seen many tumor agnostic approvals like the use of pembrolizumab in patients with MSI high regardless of histology, or type of the tumor. Another such approval is Larotrectrinib for the treatment of adult and pediatric patients with solid tumors that have a NTRK gene fusion (without a known acquired resistance mutation). The latest addition to the list of tumor agnostic approval is dostarlimab-gxly for adults with MSI high tumors based on the results of GARNET trial.[6]

For patients with localized esophageal or esophagogastric junction cancer who have residual disease in the surgical specimen after initial chemoradiotherapy, adjuvant nivolumab for 1 year has been approved recently.[7] Similarly, for renal cell carcinoma, KEYNOTE-564 showed 1 year of adjuvant pembrolizumab improved disease-free survival (DFS) compared with placebo (2-year DFS 77% vs. 68%).[8] Regulatory approval is presently pending for the same. Adjuvant nivolumab or, pembrolizumab both are already approved for the management of stage III melanoma post-surgery. Besides, adjuvant dabrafenib plus trametinib combination is also approved in patients harboring BRAFV 600E or V600K mutation.

The clinical implication of the molecular and genomic analysis is significantly dependent on the multidisciplinary decision based on joint clinic discussions having clinicians, pathologists, molecular oncologist, and bioinformatics. Despite all these advances, it should be noted that all these advanced treatments might not be delivered to patients in resource-constrained settings. To provide some relief, compassionate access programs of various pharmaceutical companies are active, however, that is not always enough and we need to do better. Instead of limiting the use of NGS in view of cost constraints, the focus should be on making it more affordable so that it can be used for the masses.

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