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Immunotherapy in Rare Cancers

Cancers that occur at a rate of fewer than six cases per one lakh people per year are defined as "Rare Cancers" by the American Cancer Society.[1] However, not all "rare cancers" meet this definition in all geographical areas uniformly, as there can be hotspots with higher incidences of these cancers. The carcinoma gall bladder is an example of this, being classified as rare cancer in the western world, whilst being one of the common causes of cancer-related mortality in women in Chile and Northern India. Although individually rare, when combined, rare cancers account for over 10% of all newly diagnosed cancers and 25% of cancer-related deaths. Rare cancers contribute to a significant proportion of cancer incidence in childhood and adolescence, accounting for two-thirds of all cancers diagnosed before the second decade of life, and one-third of cancers seen before the third decade. There are nine important rare cancers selected by the International Rare Cancers Initiative (IRCI) for collaborative research given a lack of adequate research in such cancers. These cancers are ocular melanoma, Anaplastic thyroid cancer, salivary gland cancer, penile cancer, thymoma, metastatic anal cancer, small bowel adenocarcinoma, gynaecological sarcomas and the fibrolamellar variant of hepatocellular carcinoma. It is important to remember that rare cancers do not refer to only rare histological varieties. Rather, the term also includes rare subsets of common cancers (such as the T4N0 stage of breast cancer) and rare presentations of common cancers (such as male breast cancer).[2]

The treatment of these cancers is often plagued by late or incorrect diagnoses, a lack of sufficient evidence to suggest a standard treatment protocol, or a shortfall inpatient numbers making meaningful trials difficult to conduct. The 5-year survival rate of rare cancers is 15%–20% shorter than commonly diagnosed cancers. Most of the data available on the subject are retrospective, occasionally limited to just case reports or anecdotal evidence.[1] However, the Federal Drug Administration (FDA) and the European Medicines Agency have enacted special acts such as the Orphan Drug Act and Act EC141/200 in European legislation with special grants and permissions to encourage research on therapies for rare cancers.

Cancers which are considered rare in western countries according to the definition are oftentimes not so in India. One important example is cervical cancer, which is quite common in India, whilst being equally rare in the US and the UK. Funding for research in such cancers in the West is meagre. Frequently, insurance companies in the West do not cover treatment for rare cancers unless the drug is already FDA-approved. However, since Phase III randomized control trials are not feasible for rare cancers owing to their diversity and rarity. Hence, they are not required for such drugs to be approved. For instance, Imatinib was approved for use in Dermatofibrosarcoma protuberans based on data from a Phase II trial. Unfortunately, there are no cancer groups or working committees in India which are registered for working exclusively on rare cancers at the time of writing of this article.

There are natural ways through which our immune systems culls out cancerous cells by recognizing them and attacking them through T-cells. However, Tumor cells have elaborate mechanisms to escape and survive this immune surveillance. Immunotherapy is an evolving weapon in the armamentarium of a medical oncologist. Immunotherapy drugs can potentiate weak anti-tumour responses of the immune system or can knock down the inhibitory pathways that prevent T cells to act on tumour cells. Better immunotherapy drugs are in development with a better understanding of interactions of immune cells, cancer cells and stromal cells in the immune microenvironment and with increasing knowledge about the metabolic pathways in the immune cells referred to as Immunometabolism.

The field of immunotherapy covers CART-cells, tumour vaccines, oncolytic viruses, and checkpoint inhibitors among many others. The two modalities of immunotherapy that have shown the most promise in rare cancers are checkpoint inhibitors and CAR T-cell therapies. However, when we mention immunotherapy in this article, we will be exclusively referring to immune-checkpoint inhibitors (ICIs) such as Nivolumab and Pembrolizumab.

Tumours may be classified as being immunologically hot or cold depending on the mutational load in their genome, which attracts T-cells to infiltrate them. Even after the exhaustion of all standard options of chemotherapy in advanced solid cancers in adult and pediatric patients, ICIs can still be efficacious if a gene signature called MSI-H is present.

It has been more than 30 years since ICIs first arrived on the scene. However, their real potential began to be unveiled only with the results shown by Nivolumab in 2012.

Available Evidence on Immunotherapy for Rare cancers

The breakthrough of Immunotherapy in the treatment of various common cancers (such as those of the Lung, Breast and Colon) has aroused curiosity regarding their possible use in rare cancers. There is a paucity of literature on the role of immunotherapy in rare cancers. The first such study dedicated to rare cancers was initiated in the US in January 2017 and is known

by the acronym the DART (Dual Anti-CTLA-4 and Anti-PD-1 blockade in Rare Tumors) trial. It is managed by the Southwest Oncology Group and the National Cancer Institute (NCI). This study (ClinicalTrials.gov website with identification number: NCT02834013) follows the definition of rare cancers given by the American Cancer Society. It is a tissue-agnostic Basket trial, including 53 baskets across varying tumour histologies, including carcinomas of unknown primary and not-otherwise-specified groups, which are often referred to as ultra-rare tumours. It also encompasses rare varieties of Head and Neck cancers, upper gastrointestinal, small intestinal, genitourinary, breast tumours, and soft tissue tumors.

There was no requirement for a specific biomarker-positivity to enter this study as an inclusion criterion. The drugs being studies are a combination of Ipilimumab at a dose of 1 mg/kg administered every 6 weeks and Nivolumab 240 mg IV administered every 2 weeks. The main aims of this study were to assess responses in various tumours and to analyze tumour and blood samples of patients to see how immune cells and tumour cells respond to this combination therapy. This study is still recruiting patients in various cancer subtypes and the expected study completion date is August 31, 2021.[3]

Another Phase II trial conducted by the MD Anderson institute in different types of rare cancers has shown the efficacy of Checkpoint inhibitors (47).[4] Pembrolizumab was administered every 3 weeks at a dose of 200 mg for up to 2 years as long as there was no progression or toxicity. Patients with histologically confirmed rare cancers who had progressed on standard lines of treatment with no prior exposure to PD-1/PDL-1 inhibitors were included in this study. Baseline imaging, PDL-1 testing, and tumor infiltrating lymphocytes scoring were performed.

The cancers included in this study were squamous cell skin cancer, carcinoma of unknown primary, adrenocortical carcinoma, pheochromocytoma, extra-pulmonary small cell carcinoma, Renal Medullary carcinoma, Carcinoma penis, Angiosarcoma, and Germ cell tumours, adding up to a total of 127 patients. The response rates were up to 14% and a quarter of the patients had stable disease lasting for at least 4 months. The time to treatment failure ranged from 8.1 months to 23.5 months. Better responses were seen in 4 specific cohorts of rare cancers-Squamous cell carcinoma of the skin, adreno-cortical carcinoma, Carcinoma of unknown origin and Paraganglioma-Pheochromocytoma subgroups. 1 complete response was seen in a skin cancer patient. 52% of the patients had treatment-related adverse events, among which the more commonly seen were fatigue (20%), rash (13%), hypothyroidism (11%) and anorexia (9%). Grade 3/4 toxicities included anaemia (3%), transaminitis (2%), and pneumonitis (2%).

Efficacy in Specific Cancers

The initial experiments of immunotherapy in cancer by William B Cooley was done in soft tissue sarcoma. However, there is no major approval of immunotherapy in sarcoma. Several attempts are underway to manipulate microenvironment in sarcomas, particularly to modulate Tumour-associated macrophages to be activated in the direction of pro-inflammatory and anti-tumour pathways are underway. In a rare type of sarcoma, alveolar soft part sarcoma, the combination of pembrolizumab and Axitinib has shown an objective response rate of 53%.[5]

Checkpoint inhibitors have shown good efficacy in Merkel carcinoma. Avelumab, a PDL-1 inhibitor in Phase II trial, Javelin, has shown an objective response rate of 62% with only 5% grade 3 toxicities and no grade 4/5 toxicities. Pembrolizumab has shown equally good responses with 56% response rates and a 3-year survival rate of 64%. The response rates to nivolumab in Merkel carcinoma in Phase I/II trial is 68%.[6]

There are very fewer options in recurrent glioblastoma multiforme and neoadjuvant immunotherapy has shown survival benefit compared to adjuvant immunotherapy. It was seen that Neoadjuvant therapy has conferred changes in tumour immune landscape with significant upregulation of T cell and interferon related genes.[7] Drug-resistant gestational trophoblastic neoplasia is a fatal disease and it was seen that pembrolizumab has a promising response in this disease.[8]

The other immunotherapy that is promising are CAR-T cell therapies in solid malignancies. Compared to leukaemias and lymphomas, solid tumours present several unique challenges to optimized CAR-T cell immunotherapy. For sarcomas, there is a paucity of specific and potent tumour-specific targets and high-affinity CAR-domains, the tumour microenvironment is a barrier to penetration, and both intrinsic and extrinsic inhibitory mechanisms diminish CAR-T cell longevity[9] the main limitations for research on Immunotherapy in rare cancers are the fact that most of the trials underway consists of a group of cancer histologies and results are only generalized for the entire group and cannot be concluded for a single cancer type. However, with the advent of newer adaptive trial designs and Master protocols in clinical trials, Basket trial designs, with tissue agnostic approach, a sufficient number of patients can be recruited based on a biomarker. Such trials are already underway as discussed above.

Conclusions

The Medical Oncologist needs to be aware of the resources that are available online dealing with rare cancers, such as http://www.rarecare.eu/rarecancers/rarecancers and the IRCI by NCI. These are of immense help for collaborating with other specialists and gathering adequate information for decision making on a case-by-case basis. They may also help in designing n-of-1 study protocols, developing

consortia on rare cancers, and organizing special interest oncology groups on rare cancers that may go a long way in helping both patients with these cancers and the oncology fraternity as a whole.

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