

Cancer Immunotherapy: An Impossible Dream for the Common Man?

The renaissance of cancer immunotherapy has finally happened with impressive results being achieved in hematologic and solid tumors. This has also been the defining moment for the hard-working immunologists, who were recognized by the Nobel Prize Committee in 2018 for their seminal work on understanding some of the regulatory controls of an immune response and overcoming it for therapeutic use.^[1] The flurry of activity in developing monoclonal antibodies against CTLA4, PD1-PD-L1 has resulted in Food and Drug Administration (FDA) granting approvals for Ipilimumab (against CTLA4), Nivolumab and Pembrolizumab (against PD1) and Atezolizumab, Avelumab and Durvalumab (against PD-L1), as therapeutic options in several advanced cancers.

Concurrently, the cellular adoptive immunotherapy has taken off with T-cells genetically engineered to express chimeric antigen receptor against the antigen expressed by the tumor cells (CAR-T cells), resulting in impressive results in relapsed/refractory B-acute lymphoblastic leukemia (B-ALL) and diffuse large B-cell lymphoma. These are usually fatal diseases and that long-term disease-free status has been achieved speaks of the potential for these therapies. The two CAR-T cell therapies that have been approved by the FDA are tisagenlecleucel and axicabtagene ciloleucel. A decade ago, the use of dendritic cell therapy (sipuleucel-T) was approved by the FDA for metastatic castration-resistant prostate cancer, with the therapy showing an overall survival benefit.

In addition to the above-mentioned agents, there are several more monoclonal antibodies targeting the immune checkpoint and several second and third-generation CAR-T cells in clinical trials. On the face of it, these developments are heartening since they have substantially improved the overall survival at least in a subset of patients treated. The most important cancers wherein the checkpoint inhibitors have shown good benefits are non-small-cell lung cancer (NSCLC) and melanoma. In other cancers, such as metastatic renal cell carcinoma, metastatic urothelial cancers, head and neck cancers, and hepatocellular carcinomas, the benefit in overall survival has been only a few months (usually 2–6 months) [Table 1]. Of course, in a few patients, these have translated into long-term survival benefits. While these are statistically significant benefits, they come with a price, a huge one at that.

The checkpoint inhibitors and CAR-T cell therapies come with substantial toxicity. The cytokine release syndrome (CRS) can be fatal and needs additional therapy to blockade the IL6 receptor, dialysis, and ventilatory support in some of the patients with severe CRS. In addition, neurotoxicity and B-cell aplasia (with

CD19 targeting CAR-T cell) have also been known to occur. However, the cost of the therapies can lead to financial toxicity bankrupting the family, with no insurance coverage especially in India for the total cost anticipated.

The patients' response rates have been variable and appear at least in part to depend on the immunohistochemical expression levels of PD-L1 in tumor cells and in infiltrating immune cells. The higher cutoff for the PD-L1 ($\geq 50\%$) was associated with the best response when pembrolizumab was used in NSCLC (Reck *et al.*, 2019). For other cancers and other checkpoint inhibitors, the cutoffs are different and use different reagents for the immunohistochemical assessment. This is one area which needs to be fine-tuned.

The above cost might be reduced a bit by the companies providing discounts. However, the cost could still be above Rs. 75,00,000 for the checkpoint inhibitors (1–2-year therapy) and Rs. 2,50,00,000 or above for the CAR-T cell therapies. For >99% of the Indian population, this cost is way beyond their means.

Mr. Marijn Dekkers, CEO of Bayer, had said “No, because we did not develop this product (Nexavar) for the Indian market, let's be honest. I mean, you know, we developed this product for western patients who can afford this product, quite honestly.”^[19] By and large, most of the multinational pharma companies have a similar outlook. It is therefore essential that we find our own solutions which will need to be a top-down approach identifying the centers in the country which can come together and contribute their expertise, in developing our own products.

The checkpoint inhibitors have shown significant survival benefit in metastatic NSCLC and melanomas. In other cancers where they have been approved, some patients have shown to have durable long-term disease control.

For the development of monoclonal antibodies which can bypass the patent-related issues, novel expression systems need to be assessed. These can include newer expression systems targeting different epitopes of the checkpoint proteins. Further, aptamer-based targeting is another option which is also being explored worldwide. Developing small molecule-based targeting of the immune checkpoints is another area to be explored. This will involve the supercomputing power available in the country with bioinformaticians trained in drug designing against the binding sites of the PD-1-PD-L1 proteins and then synthesizing the appropriate chemicals (excellent chemists are available in major institutions) and then evaluate the activity in appropriate *in vitro* and then *in vivo* models (excellent biologists available in several

Table 1: Clinical impact, toxicity and cost of immunotherapy agents

Cancer	Agent	Line of treatment	Overall survival	Toxicity	Cost (companies may provide discounts, which is not considered)
NSCLC	Nivolumab (Checkmate 017) ^[2]	2 nd Line	Nivolumab: 9.2 months; Docetaxel: 6 months	N: 7% D: 55%	N: US\$150,000/year (Rs. 11,250,000/year)
	Nivolumab (Checkmate 057) ^[3]	2 nd Line	Nivolumab: 12.2 months; Docetaxel: 9.4 months	N: 10% D: 54%	N: US\$150,000/year (Rs. 11,250,000/year)
	Pembrolizumab (Keynote 010) ^[4]	2 nd Line	P2: 10.4 months; P10: 12.7 months; Docetaxel: 8.5 months	P2: 13% P10: 16% Docetaxel: 35%	P: US\$150,000/year (Rs. 11,250,000/year)
	Pembrolizumab (Keynote 024) ^[5]	1 st Line PD-L1 \geq 50%	At median follow-up of 25.2 months: P: 30 months; Chemo: 14.2 months	Grade 3 to 5 P: 31.2% Chemo: 53.3%	P: US\$150,000/year (Rs. 11,250,000/year)
Head and neck cancers	Atezolizumab (Poplar) ^[6]	2 nd Line	A: 12.6 months; D: 9.7 months	A: 11% D: 39%	A: US\$13,200/month; around US\$ 158,000/year (Rs. 11,850,000/year)
	Nivolumab (Checkmate 141) ^[7]	2 nd Line	Nivolumab: 7.5 months; Treatment of physician choice: 5.1 months	Grade 3 or 4 N: 13.1% Chemo: 35.1%	N: US\$150,000/year (Rs. 11,250,000/year)
	Pembrolizumab (Keynote 048) ^[8]	1 st line	P: 11.5 months; P + Chemo: 14.7 months (in CPS>20; In CPS>1: 13.6 months); Cetuximab+Chemo: 10.7 months	Grade 3-5 P: 54.7% P + Chemo: 85% Cetuximab + Chemo: 83.3%	P: US\$150,000/year (Rs. 11,250,000/year)
	Pembrolizumab (Keynote 045) ^[9]	2 nd line	P: 10.3 months Chemo: 7.4 months	Grade 3-5 P: 15% Chemo: 49%	P: US\$150,000/year (Rs. 11,250,000/year)
Urothelial cancers	Atezolizumab (IMvigor 130) ^[10]	1 st line	A + Chemo: 13.4 months A alone: 16 months Chemo alone: 13.4 months	Grade 3-5 A: 50% A + Chemo: 91% Chemo alone: 91%	A: US\$13,200/month; around US\$ 158,000/year (Rs. 11,850,000/year)
	Pembrolizumab (Keynote 055) ^[11]	2 nd or 3 rd line	N: 25 months; Everolimus: 19.6 months	SAE N: 47.8% E: 43.6%	N: US\$150,000/year (Rs. 11,250,000/year)
Renal cell carcinoma	Nivolumab (Checkmate 025) ^[11]	2 nd or 3 rd line	N: 25 months; Everolimus: 19.6 months	SAE N: 47.8% E: 43.6%	N: US\$150,000/year (Rs. 11,250,000/year)
	Pembrolizumab plus Axitinib versus Sunitinib ^[12]	1 st line	P + Ax: 15.1 months; Sunitinib: 11.1 months	Grade 3 or above: P + Ax: 75.8% Sunitinib: 70.6%	P: US\$150,000/year (Rs. 11,250,000/year) Axitinib: US\$ 60,000/year (Rs. 4,500,000/year) Sunitinib: NATCO -US\$ 200 (Rs 15,000 for 4 weeks (28 cap of 50 mg). For 8 cycles, US\$ 1600 (Rs. 120,000) Pfizer - May offer discounts to patients). For 8 cycles of 50 mg/day for 4 weeks with 2 week break- US\$ 27,840. (Rs. 2,088,000)

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Table 1: Contd...

Cancer	Agent	Line of treatment	Overall survival	Toxicity	Cost (companies may provide discounts, which is not considered)
Melanoma	Ipilimumab ^[13]	1 st line	Ipilimumab + Dacarbazine: 11.2 months; Dacarbazine: 9.1 months		Ipilimumab: US\$ 120,000 for 4 doses (given at 3 weekly intervals) (Rs. 9,000,000)
	Pembrolizumab versus Ipilimumab (Keynote 006) ^[14]	1 st Line	P every 2 weeks and P every 3 weeks: 32.7 months; Ipilimumab every 3 weeks: 15.9 months	Grade 3-4 P (BOTH ARMS): 17% Ip: 20%	P: US\$150,000/year (Rs. 11,250,000/year) Ipilimumab: US\$ 120,000 for 4 doses (given at 3 weekly intervals) (Rs. 9,000,000)
	Nivolumab alone or in combination with Ipilimumab or Ipilimumab alone (Checkmate 067) ^[15]	1 st line	N + Ip: median OS not reached at 48 months of follow- up N alone: 36.9 months Ip alone: 19.9 months	Grade 3-4 N + Ip: 59% N alone: 22% Ip alone: 28%	Ipilimumab+Nivolumab: US\$ 256,000/year (Rs. 19,200,000/year)
Cellular therapies					
Dendritic cells	Sipuleucel-T for metastatic castration resistant prostate cancer ^[16]	2 nd LINE	Sipuleucel-T: 25.9 months Placebo: 21.4 months	Grade 3-4 Sipuleucel: 24% Placebo: 24%	US\$ 93,000 for 3 infusions given every 2 weeks. (Rs. 6,975,000)
CAR-T cells	Axicabtagene ciloleucel in DLBCL ^[17]	2 nd or 3 rd line	Median follow-up - 27 months 58% CR; Median DOR: 11.1 months; Median OS not reached; Median PFS: 5.9 months	≥Grade 3 CRS: 11%; ≥Grade 3 neurotoxicity: 32%; 2 treatment related deaths	US\$ 373,000 (Rs. 27,975,000)
CAR-T cells	Tisagenlecleucel in B-ALL ^[18]	2 nd or 3 rd line	60% CR; RFS at 12 months was 59%; EFS at 12 months was 50%; OS at 12 months was 76%	Grade 3-4: 73%; CRS IN 77%; Neurotoxicity in 40%	US\$ 450,000 (Rs. 33,750,000)

The bold fonts indicate situations wherein the overall survival benefits are more than a year. N - Nivolumab; D - Docetaxel; P - Pembrolizumab; A - Atezolizumab; E - Everolimus; Ax - Axitinib; Ip - Ipilimumab; Chemo - Chemotherapy; CPS - PD-L1 combined-positive score; PD-L1 - Programmed cell death ligand 1; CRS - Cytokine Release syndrome; DOR - Duration of response; PFS - Progression-free survival; RFS - Relapse-free survival; OS - Overall survival; CAR-T cells - Chimeric Antigen Receptor - T cells; DLBCL - Diffuse large B cell lymphoma; B-ALL - B-Acute lymphoblastic leukemia; SAE - Serious Adverse Events; 1US\$ - Rs. 75 (approximately); EFS - Event-free survival; NSCLC - Non-small-cell lung cancer

institutions). An icing on the cake would be, if known drugs are found to be effective (drug repurposing), which will cut down the time to clinical trials. This needs to be considered by the major funding agencies, bringing together a team who can be given specific responsibilities to show results in a time-bound manner. This will actually be an excellent example of interministerial collaboration with the Ministry of Electronics and Information Technology (MeitY) which has Centre for Development of Advanced Computing as one of its component units, having

the supercomputing power required for protein modeling, molecular docking, virtual high-throughput *in silico* screening, conformation analysis, etc.; Ministry of Science and Technology through the Department of Science and Technology and Department of Biotechnology; Ministry of Human Resource Development with its Indian Institute of Science and IISERs; Indian Council for Medical Research for clinical trial support, etc., It is essential that the pharma industry be involved from the beginning with the team, with a commitment like what Dr. Yusuf Hamied of Cipla

had shown in bringing out the triple drug combination of AIDS drugs at the cost of 1 US\$/day.^[20]

With regard to the CAR-T cells, developing alternate vectors is critical to keep the cost down. Further, the development of bispecific antibodies can work in a similar manner. Blinatumomab is a first-generation CD3-CD19 bispecific T-cell engager, which binds to CD19 on the surface of B cells and CD3 expressed on the surface of T cells and has been approved for relapsed/refractory ALL.^[21] There are several more in clinical trial and I am sure that the Indian scientists can rise to the occasion to develop such novel agents as well.

Of course, all this will depend on the governmental ministries/agencies coming together to plan this on a mission mode and not as a project mode and provide unrestricted funding. It needs a good team who will deliver what is entrusted to them and a committed clinical group to push it toward clinical trials. I am optimistic that it can be done, which would mean a common man can benefit from the latest developments, if not now at least in the near future.

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