Article published online: 2021-06-28

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 (≥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]	2nd 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]	2nd 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]	2nd 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]	1st Line PD-L1 ≥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)
	Atezolizumab (Poplar)[6]	2nd 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)
Head and neck cancers	Nivolumab (Checkmate 141)[7]	2nd 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]	1st 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)
Urothelial cancers	Pembrolizumab (Keynote 045)[9]	2nd 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)
	Atezolizumab (IMvigor 130)[10]	1st 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)
Renal cell carcinoma	Nivolumab (Checkmate 025)[11]	2nd or 3rd 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]	1st 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)

Contd...

Table 1: Contd...

Cancer	Agent	Line of treatment	Overall survival	Toxicity	Cost (companies may provide discounts, which is not considered)
Melanoma	Ipilimumab[13]	1st 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]	1st 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]	1st 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]	2nd 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]	2nd or 3rd 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]	2nd or 3rd 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 - Nonsmall-cell lung cancer

institutions). An icing on the cake would be, if known drugs are found to be effective (drug repurposing), which will cutdown 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.

T Rajkumar

Department of Molecular Oncology, Cancer Institute (WIA), Chennai, Tamil Nadu, India

Address for correspondence: *Dr. T Rajkumar, Department of Molecular Oncology, Cancer Institute (WIA), East Canal Bank Road, Adyar, Chennai - 600 020, Tamil Nadu, India. E-mail: drtrajkumar@gmail.com*

Submitted: 27-Apr-2020
Revised: 01-May-2020
Accepted: 14-May-2020
Published: 27-Jun-2020

References

1. Available from: https://www.nobelprize.org/prizes/medicine/2018/advanced-information/. [Last accessed on 2020 Mar 10].
2. Brahmer J, Reckamp KL, Baas P, Crinò L, Eberhardt WE, Poddubskaya E, *et al*. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. N Engl J Med 2015;373:123-35.
3. Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, *et al*. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. N Engl J Med 2015;373:1627-39.
4. Herbst RS, Baas P, Kim DW, Felip E, Pérez-Gracia JL, Han JY, *et al*. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): A randomised controlled trial. Lancet 2016;387:1540-50.
5. Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, *et al*. Updated analysis of KEYNOTE-024: Pembrolizumab versus platinum-based chemotherapy for advanced non-small-cell lung cancer With PD-L1 tumor proportion score of 50% or greater. J Clin Oncol 2019;37:537-46.
6. Fehrenbacher L, Spira A, Ballinger M, Kowanetz M, Vansteenkiste J, Mazieres J, *et al*. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): A multicentre, open-label, phase 2 randomised controlled trial. Lancet 2016;387:1837-46.
7. Ferris RL, Blumenschein G Jr., Fayette J, Guigay J, Colevas AD, Licitra L, *et al*. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. N Engl J Med 2016;375:1856-67.
8. Burtness B, Harrington KJ, Greil R, Soulières D, Tahara M, de Castro G Jr, *et al*. Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): A randomised, open-label, phase 3 study. Lancet 2019;394:1915-28.
9. Bellmunt J, de Wit R, Vaughn DJ, Fradet Y, Lee JL, Fong L, *et al*. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. N Engl J Med 2017;376:1015-26.
10. Gandhi L, Rodríguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, *et al*. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. N Engl J Med 2018;378:2078-92.
11. Escudier B, Sharma P, McDermott DF, George S, Hammers HJ, Srinivas S, *et al*. CheckMate 025 randomized phase 3 study: Outcomes by key baseline factors and prior therapy for nivolumab versus everolimus in advanced renal cell carcinoma. Eur Urol 2017;72:962-71.
12. Rini BI, Plimack ER, Stus V, Gafanov R, Hawkins R, Nosov D, *et al*. Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. N Engl J Med 2019;380:1116-27.
13. Robert C, Thomas L, Bondarenko I, O'Day S, Weber J, Garbe C, *et al*. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. N Engl J Med 2011;364:2517-26.
14. Robert C, Ribas A, Schachter J, Arance A, Grob JJ, Mortier L, *et al*. Pembrolizumab versus ipilimumab in advanced melanoma (KEYNOTE-006): Post-hoc 5-year results from an open-label, multicentre, randomised, controlled, phase 3 study. Lancet Oncol 2019;20:1239-51.
15. Hodi FS, Chiarion-Sileni V, Gonzalez R, Grob JJ, Rutkowski P, Cowey CL, *et al*. Nivolumab plus ipilimumab or nivolumab alone versus ipilimumab alone in advanced melanoma (CheckMate 067): 4-year outcomes of a multicentre, randomised, phase 3 trial. Lancet Oncol 2018;19:1480-92.
16. Small EJ, Schellhammer PF, Higano CS, Redfern CH, Nemunaitis JJ, Valone FH, *et al*. Placebo-controlled phase III trial of immunologic therapy with sipuleucel-T (APC8015) in patients with metastatic, asymptomatic hormone refractory prostate cancer. J Clin Oncol 2006;24:3089-94.
17. Locke FL, Ghobadi A, Jacobson CA, Miklos DB, Lekakis LJ, Oluwole OO, *et al*. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): A single-arm, multicentre, phase 1-2 trial. Lancet Oncol 2019;20:31-42.
18. Maude SL, Laetsch TW, Buechner J, Rives S, Boyer M, Bittencourt H, *et al*. Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia. N Engl J Med 2018;378:439-48.
19. Marijn Dekkers Comments. Available from: https://archives.cjr.org/the_audit/bloombergs_viral_misquote_1.php.

20. Lane R. Yusuf hamied: Leader in the Indian generic drug industry. Lancet 2015;386:2385.
21. Przepiorka D, Ko CW, Deisseroth A, Yancey CL, Candau-Chacon R, Chiu HJ, *et al*. FDA Approval: Blinatumomab. Clin Cancer Res 2015;21:4035-9.

Access this article online

Quick Response Code:

Website: www.ijmpo.org

DOI: 10.4103/ijmpo.ijmpo_199_20

How to cite this article: Rajkumar T. Cancer immunotherapy: An impossible dream for the common man? Indian J Med Paediatr Oncol 2020;41:312-6.