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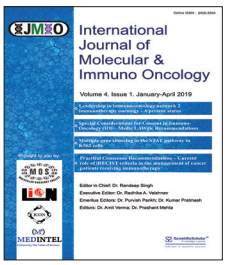
International Journal of Molecular and Immuno Oncology



Original Article

Special considerations for consent in immuno-oncology - Medic LAWgic recommendations

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Received : 31 December 2018
Accepted : 01 January 2019
Published : 16 February 2019

DOI
10.25259/IJMIO-3-2019

Access this article online
Quick Response Code:

ABSTRACT

Novel immuno-oncology medications are a new addition to the armamentarium in the fight against cancer. This new class of drugs have unique toxicities whose understanding is constantly evolving. Today more is published in scientific literature every year then we can test in our lifetime. Hence we need to take advantage of existing technology to improve the experience of the healthcare team as well as the patients and care givers while going through available literature and information. This will improve understanding and empower the patients to participate actively in the decision making process. This manuscript is an initiative to achieve this objective.

Keywords: Toxicity, Checkpoint inhibitors, Lung cancer, Breast cancer, pdl1, Counselling, Communication, Regulatory compliance

2019 Published by Scientific Scholar on behalf of International Journal of Molecular & Immuno Oncology.

INTRODUCTION

There is increasing awareness that every patient has the right to full information to make a real decision.[1] This is possible when the patient can understand the diagnosis, treatment, prognosis, alternatives, possible complications, and risks. This will empower the patient to be part of the decision-making process in a logical and fair manner.

The Supreme Court of India, in its judgment dated January 16, 2008, for the case of Samira Kohli versus Dr. Prabha Manchanda and Anr (Case No Appeal [civil] 1949 of 2004), made a statement that questions the use of costly medicines (among other things).[2] Since most immuno-oncology (IO) drugs are expensive, the expectations (in the minds of patients) tend to be unrealistically optimistic - equating expense with better chance of benefit. In any case, a separate written consent is required when using new techniques or drugs, as per IMCR 2002 Regulations.[3] Hence, hypothetically, even if a novel IO drug being used is an oral medication, it is recommended that written consent be taken and documented.

The first modern IO drug to receive approval for marketing in the USA (by the US Food and Drug Administration [FDA]) was as recent as in March 2011.[4] This was for Ipilimumab (brand name Yervoy) in metastatic melanoma patients. On December 22, 2014, the FDA first granted regular approval to the anti-PD1 monoclonal antibody, Nivolumab (brand name Opdivo/Opdita) for use in humans with cancer.[5] Subsequent approvals for additional indications for this same drug were given 11 times over the next 3 years (in March 2015, October 2015, November 2015, January 2016, May 2016, November 2016, February 2017, August 2017, September 2017, and December 2017).[5] Moreover, at least 10 other

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Table 1: Salient important features from the package insert (information approved by regulatory authorities and to be provided by manufacturer with the drug as a mandatory compliance requirement) of Nivolumab.

a. This medicine is subject to additional monitoring
b. Read all of this leaflet carefully before you start using this medicine because it contains important information for you
c. If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet
d. You should not take OPDIVO if you are allergic to Nivolumab or any of the other ingredients of this medicine
e. OPDIVO may cause
  i. Problems with your lungs such as breathing difficulties or cough due to inflammation of the lungs (pneumonitis or interstitial lung disease)
  ii. Diarrhea (watery, loose, or soft stools) or any symptoms of inflammation of the intestines (colitis) such as stomach pain and mucus or blood in stool
  iii. Inflammation of the liver (hepatitis)
  iv. Inflammation or problems with your kidneys
  v. Problems with your hormone-producing glands
  vi. Diabetes
  vii. Inflammation of the skin that can lead to severe skin reaction (known as toxic epidermal necrolysis and Stevens–Johnson syndrome)
  viii Inflammation of the muscles
f. Please note that these signs and symptoms are sometimes delayed and may develop weeks or months after your last dose. These complications can be severe and can lead to death
g. Your doctor will continue giving you OPDIVO for as long as you keep benefitting from it or until you no longer tolerate the treatment
h. Do not stop treatment with OPDIVO unless you have discussed this with your doctor.

Table 2: List of websites that can be trusted to provide reasonably unbiased and/or up to date information regarding IO drugs and treatments

a. Regulatory authorities and other governmental bodies
  i. CDSCO - www.cdsco.nic.in
  ii. DCGI - www.cdscoonline.gov.in/www.cdsco.gov.in
  iii. NCI USA - www.cancer.gov
  iv. US FDA - www.fda.gov
b. Medical societies and associations
  i. ICON Trust - www.oncologyindia.org
  ii. ISMPO - www.ismpo.org
  iii. NCCN - www.nccn.org
  iv. ASCO - www.asco.org
  v. ESMO - www.esmo.org
  vi. Cancer.Net - www.cancer.net
c. NGOs
  i. Web MD - www.webmd.com
  ii. Kidney Cancer - www.kidneycancer.org
  iii. CPAA - www.cpaaindia.org
  iv. ICS - www.indiancancersociety.org
d. Scientific publications
  i. IJMS - www.ijmsweb.com
  ii. IJMIO - www.ijmio.com
  iii. JDHC - www.jdhc.info
  iv. IJMR - www.ijmr.org.in
  v. IJMPO - www.ijmpo.org
e. Drug information on manufacturing pharma companies websites
  i. AZ - www.azimmuno-oncology.com
  ii. Pfizer - www.pfizer.com/science/oncology-cancer/immuno-oncology
  iii. Merck - www.merck.com/product/oncology/home.html
  iv. BMS - www.immuno-oncologynews.com/tag/bristol-myers-squibb
  v. BI - www.boehringer-ingelheim.com/innovation/therapeutic_areas
  vi. Novartis - www.novartis.com/our-company/novartis-oncology

IO drugs received approval in 2018 alone. This is in addition to the 300+ global clinical trials ongoing in the field of IO. In fact, James Allison and TasukuHonjo won the Nobel Prize in Medicine for their research on cancer immunotherapy only the past year (2018).[6] Hence, there is no doubt that IO is a new field and IO drugs require written consent for the time being.

There are specific items that can be included as part of consent on the 1st day of registration or visit to the doctor. These aspects can be accessed from our article in the Indian Journal of Medical Sciences and are developed to ensure that both parties understand what to expect from each other, creating a better transparent and robust feedback system.[7] These aspects will not be discussed in the current manuscript.

While most of the consent process should be in the lay terms using simple words that the patient can easily understand, there are aspects of the consent that is recommended to include exact medical scientific terms.[7] This refers to the diagnosis/disease/ailment, treatment planned, other standard treatment options (if any), and possible complications.

The special circumstances with respect to IO drugs which will be the focus of the rest of this recommendation are limited to treatment planned, other standard treatment options, and possible complications.[8]

- For treatment planned, the features of importance are the intended benefit, need for regular follow-up, evaluating response, and duration of treatment. IO treatment usually benefits only a small percentage of patients; responses can be delayed; treatment decisions are based on evaluation on regular basis, and hence, frequent regular follow-ups are required; responding patients are expected to have symptom control and prolongation of life but not cure; the treatment is supposed to be continued indefinitely in patients that respond and who can tolerate the drug - are points that need to be included in the informed consent.[9]
- As far as complications are concerned, overall, requirements of real consent are available elsewhere. As far as IO drugs are concerned, this is a dynamic area. We are still learning how the human body reacts to them. Hence, there is a real possibility of side effects and complications that we are currently not familiar with. Complication can also be life threatening. Patients should, therefore, be cautioned to report promptly in case of any new medical feature/ailment or if the general condition worsens[10] [Table 1].
- Normally, cost should not be a consideration while deciding a patient's treatment. However, in India (and most low and middle-income countries), patients are not covered by insurance and have to pay for treatment from their own pocket. Hence, discussion regarding cost is important to complete patient's understanding. While it will not be part of

the written informed consent, documentation in the patient medical records is recommended that cost implications have been understood by the patient especially in view of the prolonged and indefinite duration of treatment with IO drugs.[11]

- Use of technology empowers patients and helps them to make the choices that they prefer - Google translate (and its app) can be used for international patients.[12] It can also help patients who do not understand English, Hindi, or language that their doctor speaks. The return of the Google translate application programming interface for a modest fee of USD 0.05 per page is most welcome.[13] Technology can also help prevent common problems of patients not remembering everything that was told to them, patients focusing on and recalling only what they wanted to hear in the first place (usually positive aspects), as well as conflicting understanding among the patient and family members.[14]

Patients and family members (at least the educated ones and those with access to internet) almost always explore information about their illness online. Unfortunately, the internet is without peer review, and hence, a lot of biased or anecdotal personal experiences are available and distort the real picture. We can empower the patient and family by providing a list of websites that can provide information in a reliable manner. List of trusted websites can include for IO drugs and treatments are shown in Table 2.[15]

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