Rajiv Gandhi Cancer Institute and Research Centre

NewsLetter

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EDITORIAL

HUMILITY: THE ESSENCE OF MEDICAL PRACTICE

Humility is the medical virtue most difficult to understand and practice. This is especially true in contemporary medicine, which has developed a culture more characterized by arrogance and entitlement than by self-effacement and moderation. Nowadays, humility is hardly a valued ideal. The word "good physician" calls up an image of confidence, technical skill, and assertiveness, a cluster of characteristics that seem inconsistent with humility. In today's medical culture, humility appears weak, wishy-washy, counterproductive, or even deceptive. Moreover, patients themselves are likely to question the competence of doctors who too quickly acknowledge their own limitations. The Oxford English Dictionary defines humility as "the quality of being humble". Wikipedia states: humility is "the quality of being modest, reverential, even politely submissive, and never being arrogant, contemptuous, rude."

I consider four distinct but closely related personal attributes of humility

1. Unpretentious openness: The first and most obvious feature of humility as a professional virtue is acceptance of one's limitations or one's own deficiency .To function within your own capabilities, you first have to be aware of what you are, to assess your personal strengths and weaknesses realistically, as well as your medical knowledge and abilities.

2. Avoidance of arrogance: Many believe that arrogance is more pervasive and characteristic of today's medical persona. Physician arrogance is a flaw, but it is avoidable

3. Honest self-disclosure: A third feature associated with humility is honesty, especially about your mistakes. How many of us report our own medical errors. We try to manipulate the facts because of fear of litigation. We would rather accept our privileged status in life. "An effective apology is one of the most profound healing process between individuals."

4. Modulation of self-interest: A final feature of humility is the ability to maintain inner balance and to modulate self-interest. The good doctor is motivated to down-regulate his personal interests (e.g., convenience, peer approval, pleasure, financial gain, power, or prestige) when it is in his patients' best interests. Good physicians put the interests of their patients ahead of self-interests.

My hypothesis is that physicians who cultivate unpretentious openness, honest disclosure, and modulation of self-interest, and who avoid arrogance, have demonstrated humility. These days hospitals compete relentlessly for market share, trumpeting their leading-edge facilities and outstanding medical staffs. Their advertisements scream: our doctors are the best in the nation! We have the world's finest cancer specialists! We're ranked #1 in cancer surgery! Have you ever seen a full-page advertisement in the Times of India headlined with these words:" **our doctors rank among the most humble in India".**

We hardly admit our mistakes, we rarely acknowledge our limitations! As I continue my medical training, I am constantly reminded that medicine is so much bigger than me. Being a physician really is not about obtaining my own personal goals. It has to be about serving others and restoring life. Why is humility in medicine so important? Because in order to be excellent physicians, we must truly understand and value the patient. And at the end of the day, you cannot effectively treat a patient's mind, body and soul if you do not see their inherent worth as human beings. A medical student can be bright, well read and demonstrate above average skills but unaccepting of criticism or feedback. He possesses many gifts but lacks humility. If asked to describe the characteristics of an excellent physician, many of us probably would not include humility at the top of the list. The humble physician is not ashamed to admit ignorance and is not too proud to request assistance from fellow consultants. The experienced physician senses the deep mysteries of the practice of medicine, both on the biologic side and the humanistic side. The humble physician is never satisfied .that he knows enough medicine or that he knows everything about his patient. One of the least-heard phrases at an academic medical center is "I don't know." Even rarer are the statements "I was wrong" or "I made a mistake." Nonetheless, it takes a humble, self-effacing physician to admit a mistake. By the time the patient reaches the hospital he is already humbled (some would say humiliated) by disease or the medical care system. The humbled patients search for humble doctors. But patients may meet skilled technocrats with no humility.

As Scottish author J.M. Barrie wrote, "Life is a long lesson in humility." Sir William Osler understood that while some things can be known, others must be inferred or experienced. One morning, Osler was seen. "Struggling in the effort to pass a stomach tube upon himself, resulting in the ordinary gagging and retching". When asked what he was doing, he replied: "Well, we often pass these tubes on people, and I thought we ought to find out what it feels like ourselves." Wisdom led Osler to appreciate those things that characterize human vulnerability and patienthood; humility helped him understand that there are aspects of human suffering that are not easily penetrable. "This grace of humility," Osler wrote, "is a precious gift." How physicians see patients or, more specifically, how patients perceive themselves to be seen can influence their sense of dignity. Physicians who lack humility talk at their patients; physicians who are sufficiently humble talk with their patients. Perhaps most humbling of all is accepting that anyone can make a mistake. While this can happen to any physician, most worrisome are those who don't know what they don't know.

The cultivation of humility is often painful and requires a high level of self awareness and reflective practice but I can't say exactly when I learned perhaps the most important trait of being a doctor: humility. I can, however, recount numerous times when I've been humbled in medicine, which I suppose over time have instilled a sense of humility into my practice and my personality. One of these "character-building" episodes most prominent in my memory was the first time during my early service days. I always aspired to acquire latest knowledge and technical skills. My seniors encouraged me to do newer procedures at every opportunity. Once my teacher & mentor told me to do a palliative mastectomy for bleeding sarcoma breast in young girl. I took up the case overconfidently in late evening without an anesthetist and with just one unit of blood in hand. As I gave local anesthetic agent, she had status epilepticus and I could not save the patient. First time in my early medical career, I cried like a child infront of father of diseased girl. "I don't know what happened, but I lost her, I am sorry "I said sobbing. Same night I went to my boss's house and narrated the incident. I wept for long. My boss gave me first lesson "Don't be overconfident. Surgery is not heroism, it is humbleness." Late night with tears in my eyes, I could not sleep. This incident mellowed me down and I started thinking "what if I am sitting on the other side of the table". I also learned not to be afraid to ask for help when things aren't going my way, or the patient's, and to let one of my friend/colleagues come to the rescue without permanently damaging my sense of self-worth. Medicine is a humbling profession, and we work in a difficult environment with lives on thin line.

Dr. A. K. Dewan
Director - Surgical Oncology

IMMUNOTHERAPY: A NEW ROADMAP TO CHILDHOOD CANCER

Cancer immunotherapy, also known as immuno-oncology, is a form of cancer treatment that uses the power of the body's own immune system to prevent, control, and eliminate cancer.

The fields of immunology and oncology have been linked since the late 19th century, when the surgeon William Coley reported that an injection of killed bacteria into sites of sarcoma could lead to tumor shrinkage. Since that time, exponential advances in the understanding of the intersection between immune surveillance and tumor growth and development have led to broad therapeutic advances that are now being studied in all cancer types.

Also, the advances in cancer biology and pathogenesis during the past two decades have resulted in immunotherapeutic strategies that have revolutionized the treatment of malignancies, from relatively non-selective toxic agents to specific, mechanism-based therapies. The genetic landscape and biology of childhood cancer is quite different from adults, and hence their behaviour and response to treatment also varies.

Cancer immunotherapies, widely heralded as transformational for many adult cancer patients, are becoming viable options for selected subsets of paediatric cancer patients.

Many therapies are currently being investigated, from immunomodulatory agents to adoptive cell therapy, bispecific T-cell engagers, oncolytic virotherapy, and checkpoint inhibition. The current article highlights few of the former being used in paediatric cancer, which have changed the face of cancer treatment in children in frontline as well as relapsed setting.

Targeted Antibodies

Blinatumomab:

- Blinatumomab is a bispecific T-cell engaging (BiTE) antibody linking the targeting regions of two antibodies directed against CD19 and CD3, approved for subsets of children with acute lymphoblastic leukemia (ALL).
- Mechanism of action: CD19 is expressed by the precursor-B-ALL cells, and CD3 is the constant part of the T-cell receptor (TCR) complex that mediates T-cell receptor signaling. Blinatumomab, therefore, leads to a very close linkage between malignant B cells and T cells, a cytolytic synapse forming in the close contact zone. The strong activation of engaged T cells leads to direct and serial lysis. Furthermore, blinatumomab induces the polyclonal proliferation of activated T cells, which leads to an increased activity of blinatumomab 1 to 2 days after the onset of application. (figure 1)
- Cytokine release syndrome (CRS) and neurotoxicity are the most feared adverse events under therapy with blinatumomab

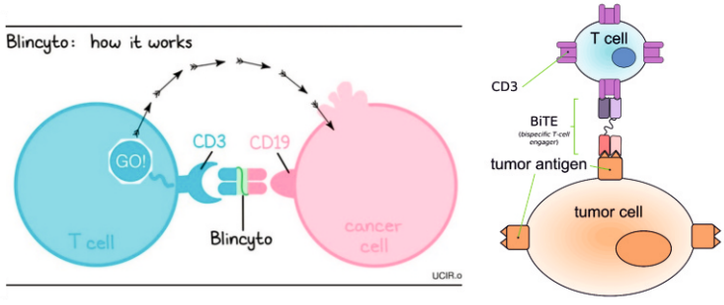

Figure 1: Mechanism of action of blinatumomab (for acute lymphoblastic leukemia)

- The if's and but's: All available data in R/R-ALL suggest a necessity for HSCT after a bridging therapy with blinatumomab. Ongoing trials will show whether blinatumomab is capable of inducing lasting remissions without a following allogeneic HSCT or constitutes a suitable maintenance therapy post-HSCT. Adult data suggest that not all MRD responders necessarily require a transplant

Inotuzumab:

Inotuzumab ozogamicin (InO) is a CD22-directed humanized monoclonal antibody conjugated to the potent cytotoxin calicheamicin. CD22 is widely expressed on B-ALL blasts and is rapidly internalized upon antibody binding, making it an excellent target for immune-targeted chemotherapy in B-ALL (figure 2).

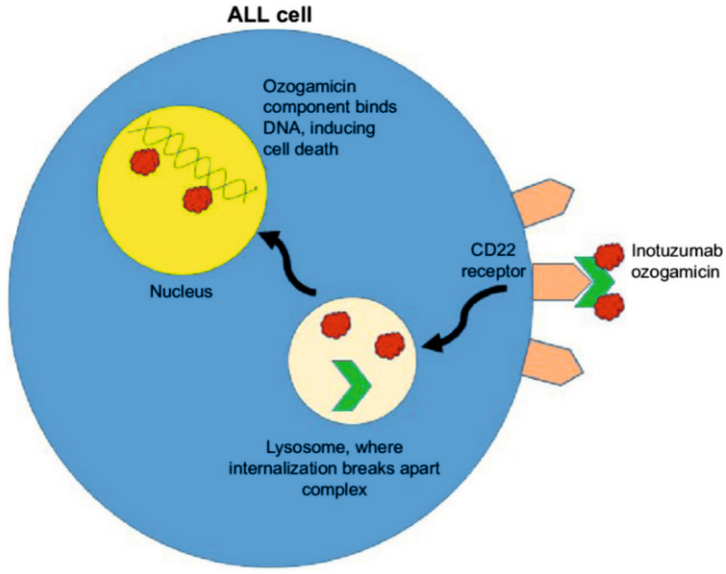

Figure 2: Mechanism of action of Inotuzumab (for relapsed refractor ALL)

- The if's and but's: In the randomized phase 3 clinical trial(INO-VATE ALL) on which the approval was based in 2017, had more than 300 patients .The study showed encouraging results in relapsed and refractory ALL. However, robust prospective data on the efficacy and safety of InO in pediatric pts is lacking. Cytokine release syndrome (CRS) and sinusoidal obstruction syndrome (SOS) are the most feared adverse events under therapy with InO.

Dinutuximab: Dinutuximab beta is a monoclonal antibody that targets disialoganglioside 2 (Gd2), which is ubiquitously overexpressed on neuroblastoma

- Neuroblastoma (NB) is the most common extra cranial solid tumor of childhood, with 60% of patients presenting with high risk (HR) NB by means of clinical, pathological and biological features. The 5-year survival rate for HR-NB remains below 40%, with the majority of patients suffering relapse from chemorefractory tumor. Immunotherapy is the main strategy against minimal residual disease and clinical experience has mostly focused on monoclonal antibodies (MoAb) against the glycolipid disialoganglioside GD2.

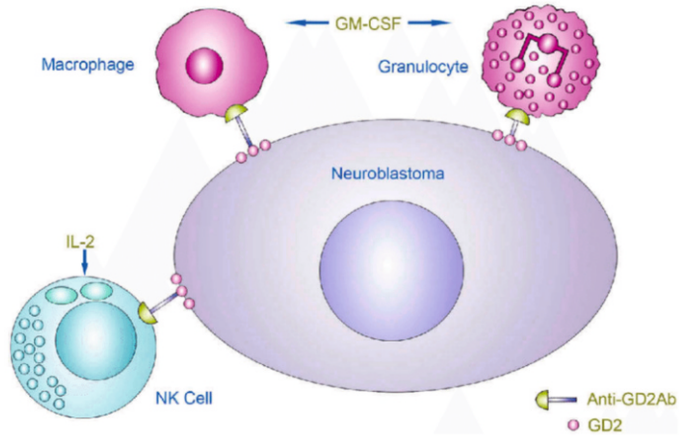

Figure 3: Mechanism of action of Dinutuximab (for Neuroblastoma)

- The combination of cytokines IL-2 and GM-CSF with the anti-GD2 MoAb ch14.18 (Dinutuximab) has shown a significant improvement in outcome for HR-NB. The FDA and EMA approved dinutuximab (Unituxin(R)) in 2015 and European Medicines Agency in 2017 for the treatment of patients with HR-NB who achieved at least a partial response after multimodality therapy.

- The Ifs and Buts: Despite its efficacy in HR Nb, most studies were unable to combine it with other standard immunotherapy like (13-cis retinoic acid) during maintenance therapy due to its toxicity profile. Most common adverse effect encountered are capillary leak syndrome, hypotension, myalgia and urticaria .

Immunomodulators

Immunomodulators are molecules that act on the pathways that regulate the immune system's activity. They act on the brakes and gas pedals of the immune system. The modulation of the former allows developing therapies that can target both in order to improve the immune system's ability to attack and eliminate cancer. With respect to the different types of Immunomodulators, they can be roughly divided into four categories: checkpoint inhibitors, cytokines, agonists, and adjuvant. Some of the important ones, been used in paediatric cancer are as follows:

- **Ipilimumab:** a checkpoint inhibitor that targets the CTLA-4. Blockade of CTLA-4, allows uninterrupted cytotoxic action of T cells on tumor cells. It is approved for subsets of paediatric patients with advanced melanoma. However many phase 1 and 2 trials are on way for Sarcoma, Wilm tumor, lymphoma, neuroblastoma.

- **Nivolumumab and Pembrolizumab:** a checkpoint inhibitor that targets the PD-1 pathway; approved for subsets of paediatric patients in various solid tumors , especially Hodgkins lymphoma, where it is being used as monotherapy, combination therapy in frontline as well as relapsed setting . However robust paediatric trials are underway. The blockade of PDL1, causing PD1 and PD2 pathway inhibition allows uninterrupted cytotoxic action of T cells.(figure 4).

Interestingly, PD-L1 and PD-L2 ligands are structurally similar and both can suppress T cell activity, but they differ in their distribution throughout the body. PD-L2 has a more limited distribution, including macrophages and dendritic cells. The mRNA of PD-L1 is in almost all human tissues in addition to various malignant cells, possibly a mechanism for the immune system to recognize every cell in the body.

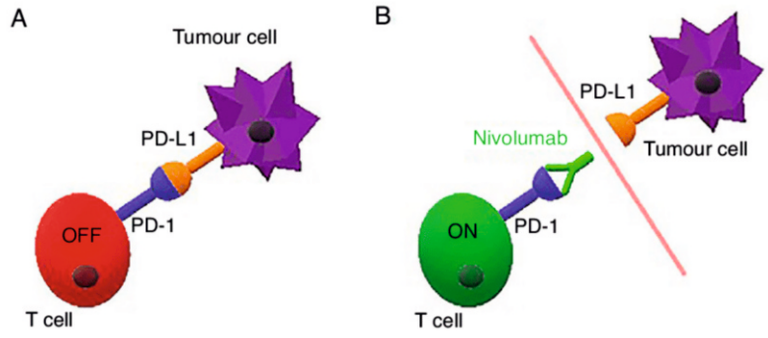

Figure 4: Mechanism of action of PD1/PDL1 Inhibitors (for pediatric solid tumors and Hodgkin lymphoma)

The Ifs and but: PD-L1 and PD-L2 expression has been found to be relatively low in many paediatric solid tumors. Furthermore, the checkpoint inhibition–induced augmented immune response is associated with a distinct pattern of side effects and toxicities, also known as immune-related adverse events.

Adoptive Cell Therapy

CAR T cell therapy:

- Chimeric antigen receptors (CARs) are recombinant receptors for antigens which redirect the specificity and function of T lymphocytes and/or other immune cells in a single molecule. The concept of using CARs in cancer immunotherapy is that CARs, which are programmed targeting tumor-associated antigens, can be replicated rapidly and homogeneously. Direct infusion of these armed tumors targeting T-cells bypass the barriers and kinetics of active immunization.

- Mechanism of action: T cells harvested from peripheral blood are transduced with genetically engineered CARs that render the ability to recognize cancer cell-surface antigen and lyse cancer cells. The successes in CAR T-cell therapy for B-cell leukemia and lymphoma have led to efforts to expand this therapy to solid tumors (figure 5).

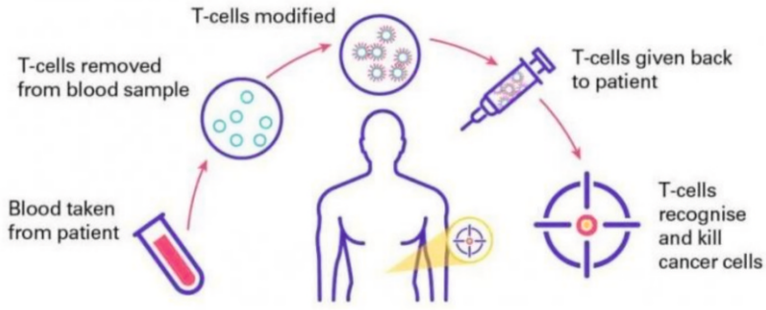

Figure 5: Conceptualisation and functioning of CAR T cells therapy

The ifs and buts: Despite its popularity and effectiveness in refractory and multiply relapsed patients, - cost, availability, standardisation and validation of procedure remains a big obstacle.

The adverse effects associated are Cytokine release syndrome (which can be life threatening). Few institutes in India have also started CAR T cell under trial basis, which seems promising, yet a long way to go.

TAKE HOME MESSAGES

1. Immunotherapy exploits the body's own immune system to fight cancer cells, which may be by means of antibodies, T cell pathways, NK cells or vaccines.
2. It has given a ray of hope to otherwise some of the incurable paediatric malignancies.
3. It may transform the way we treat childhood cancer today with less toxic therapies.
4. Predictive biomarkers remain a caveat.
5. Cost and availability are major concerns in India today

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