ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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Dosing of Nivolumab in India

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H&O What factors determine the appropriate dose of nivolumab?

VN The dosing of any drug is determined by multiple factors. Traditionally, drug dosing is initially determined by studying the drug in vitro to determine the pharmacokinetics, the pharmacodynamics, the affinity of the drug for its receptor, and the elimination of the drug. This also includes determining whether the drug is renally cleared or whether it is hepatically cleared. All this information is used to study the initial dosing of the drug.

After the initial in vitro studies, we move on to phase 1 studies. In phase 1 studies, the focus is on escalating the drug dose sequentially until the patient can tolerate no more, which is the maximum tolerated dose. From there, that dose is usually lowered according to clinical determination of tolerance to toxicity. The lower dose is the recommended phase 2 dosing.

This dosing approach has traditionally been used for chemotherapeutic drugs. However, it does not hold true for a lot of modern drugs, including targeted therapies, oral tyrosine kinase inhibitors (TKIs), and immunotherapies such as the checkpoint inhibitor nivolumab (Opdivo, Bristol-Myers Squibb). Nivolumab binds to the programmed death 1 (PD-1) protein that is present on T cells, and receptor occupancy occurs at a very low dose. As a result, increasing the dose of the immunotherapy does not increase receptor binding. Instead of following the typical dose-response curve, nivolumab plateaus at a low level and then gets eliminated.

Normally, 70% to 75% of the PD-1 receptor needs to be occupied for nivolumab to be effective. This occurs at a dose of 0.3 mg/kg, which is just one-tenth of the usual administered dose of 3 mg/kg.

H&O Could you describe the randomized study of low-dose nivolumab in head and neck cancer?

VN A decade ago, we had few drugs available to treat advanced head and neck cancer. At that time, we relied on intravenous chemotherapy, but responses were low and toxicity was high. Advanced head and neck cancer also gets divided into platinum-refractory and platinum-sensitive categories. Patients with platinum-sensitive head and neck cancer are expected to respond to platinum-based chemotherapy. However, patients with platinum-refractory disease, who have received platinum in the curative setting or in the first-line palliative setting and then have disease recurrence within 3 to 6 months, do not respond to most treatments and have a very poor prognosis.

In these patients, immunotherapy initially showed some efficacy, but it was not remarkably effective. Unfortunately, immunotherapy is extremely expensive in India and is not affordable for more than 95% of the population, making it impossible to deliver standard-of-care therapy to most patients. In the platinum-sensitive setting, pembrolizumab (Keytruda, Merck) was added to chemotherapy and became the standard of care based on the results of KEYNOTE-048. Because delivering standard-of-care therapy was not feasible for most of our Indian patients with advanced head and neck cancer, we devised a regimen consisting of oral metronomic chemotherapy, which

involves administering oral chemotherapy more frequently and at lower doses than conventional chemotherapy. This minimally toxic approach acts via nontraditional cytotoxic methods, including anti-angiogenic activity and activating the tumor–directed-immune response.

We found that advanced head and neck cancer has a good response rate to oral metronomic chemotherapy, but the response is not sustained. When we thought about how to best sustain the response, we came up with the idea of adding immunotherapy. However, adding immunotherapy at full dose was not possible owing to the high cost of the drug, which also would have affected our ability to obtain funding for the study. Therefore, we decided to look at the dosing and opted for low-dose immunotherapy.

The study, which was led by Drs Kumar Prabhash and Vijay Patil, was published in the *Journal of Clinical Oncology* in 2023. Patients in the study were randomly assigned 1:1 to triple metronomic chemotherapy (TMC) consisting of oral methotrexate once a week, celecoxib twice daily, and erlotinib (Tarceva, Astellas) once daily vs TMC with intravenous nivolumab (TMC-I) at a dose of 20 mg intravenously once every 3 weeks. We required 150 events to evaluate 1-year overall survival (OS), which was the primary endpoint of the study. The study was designed as a superiority trial and enrolled 150 adults with newly diagnosed head and neck cancer, regardless of whether it was platinum-sensitive or platinum-refractory. The patients had to have an European Cooperative Oncology Group performance status of 0 to 1 at any site, with the oral cavity being the predominant site in our country, although we did not restrict enrollment to that site.

We found that the primary endpoint significantly improved with the addition of low-dose nivolumab. The 1-year OS increased from approximately 16% in the TMC arm to 45% in the TMC-I arm. The addition of low-dose immunotherapy also improved almost all other efficacy parameters, including the response rate, progression-free survival (PFS), and quality of life. Furthermore, it did not increase the toxicity significantly. We concluded that TMC-I improved OS and is an effective regimen for our patients.

Was it the best study that we could have done? Perhaps not. If we had unlimited resources and could do the optimal study, we would have compared low-dose immunotherapy with or without chemotherapy to the standard-of-care regimen, which is full-dose immunotherapy with or without chemotherapy, like the KEYNOTE-048 study. We also could have compared it to chemotherapy plus cetuximab (Erbitux, Lilly; eg, the EXTREME regimen). Unfortunately, these are not affordable regimens in our setting. Thus, TMC-I has become a standard of care for patients who cannot afford globally approved dosing of immunotherapy.

H&O Are there any other studies that have investigated nivolumab, and what clinical trials are currently ongoing?

VN We started using low-dose immunotherapy earlier, based on a retrospective analysis from Korea by Yoo and colleagues on the use of low-dose nivolumab in patients with non–small cell lung cancer (NSCLC) who could not afford standard nivolumab treatment. They found it to be as effective as full-dose immunotherapy, but the sample size was very small (n=47). In fact, they observed a numerically slightly higher PFS and OS in the patients who received low-dose nivolumab. Although this was a retrospective analysis, it gave us confidence that clinicians can use this dosing in routine practice.

> As investigators, institutions, and funding agencies, we must recognize that our responsibility is to the patient, and it is up to us to ensure that these trials get funded appropriately and are designed and implemented effectively.

Multiple other studies are ongoing at different locations for several tumors with various dosing regimens. In our center, we are doing a broad study with a sample size of approximately 800 patients called Development of Low-Dose Immunotherapy in India (DELII); the principal investigator is Dr Rajendra Badwe. We are comparing the use of low-dose immunotherapy vs physician's choice of therapy in patients who have relapsed disease from multiple primary tumors, such as head and neck cancer, lung cancer, bladder cancer, triple-negative breast cancer, and any tumor with high microsatellite instability or mismatch repair deficiency. We have also expanded low-dose nivolumab to the first-line setting. We have published data on the use of nivolumab in head and neck cancer in the first-line setting, but we are also evaluating it in low-dose immunotherapy in NSCLC using pembrolizumab, which is more commonly used. Additionally, several other

studies have been submitted to or just approved by ethics committees. This concept has sparked the imagination of a lot of investigators, and I anticipate in the coming years, we will learn much more about the appropriate and optimal dosing of immunotherapy.

H&O How does the cost of nivolumab affect patient access to treatment, and what measures are being taken to address this issue?

VN A couple of years ago, we audited approximately 5000 to 7000 patient records to identify patients who had an approved indication for immunotherapy; we found that only 1.6% were able to afford it. When we expanded the audit a couple of years later, that percentage had increased to 2.8%. The percentage went up because we started using low-dose immunotherapy, but even low-dose immunotherapy is unaffordable for most patients. The first step toward bridging that affordability gap is to evaluate alternative dosing regimens using far lower doses, such as one-tenth of the standard dose, or vial sharing. In our study, we shared a 40 mg vial of nivolumab between 2 patients, each receiving a dose of 20 mg. Initially, we had difficulty getting funding for the low-dose immunotherapy trial. It was supported by our institution, and funded by a local oncology society, and individual philanthropy—Motivation for Excellence, which had been founded by one of our patients who understood and supported what we were trying to do.

We will also explore the use of generic immunotherapy drugs, which will become available in a couple of years. Although costs are not expected to dramatically fall in the near future, we have to investigate alternative mechanisms of improving access.

H&O What are reasons for the low accessibility of nivolumab in low- and middle-income countries, and what challenges do they face in providing access to cancer treatment?

VN The challenge is financial toxicity. There are also accessibility challenges in a few other countries, just not as much as India. Although we have the drugs available, they are just not affordable. I believe it is a moral obligation to ensure that anything efficacious found in a trial is made available to those who need it, regardless of where they live. As those who treat patients with cancer, it is our responsibility to ensure that we get efficacious treatment to all who need it. This is where research comes in. However, the issue is that it needs to be financially viable for the companies producing the drugs. Although I do not know the details of pricing and marketing, these are commercial organizations. As investigators, institutions, and funding agencies, we must recognize that our responsibility is to the patient, and it is up to us to ensure that these trials get funded appropriately and are designed and implemented effectively. Unfortunately, conducting research is difficult. There are a whole lot of reasons why there are not as many research studies done in India as the rest of the world. If you do not have the funding or the infrastructure, even the best study in the world will not happen. I think it is essential to give publicity to what we are doing and make people understand that this needs to be done.

H&O How might the results of your study affect the use of PD-1 inhibitors in general, and nivolumab in particular?

VN The comparator in our study was not full-dose immunotherapy, so I am not entirely sure that the results affect strategy. We do not know for sure whether low-dose immunotherapy is similar to full-dose immunotherapy. According to all the preclinical data, in vitro, and pharmacokinetic-pharmacodynamic data, it looks like it is, but we do not have definitive evidence of this. I am not sure who would fund a study comparing full-dose vs low-dose immunotherapy. It would definitely be a challenge to secure funding for such a study. However, I think the data are provocative, and we need to see whether this can eventually become the standard of care globally. How we are going to do that, I am not entirely sure, but perhaps a global movement and more interest of funding agencies could make it possible to conduct such a study.

H&O Is there anything else you would like to add?

VN This is a push to provide effective drugs to all patients who might benefit, and it is not just limited to immunotherapy. For example, the oral TKI osimertinib (Tagrisso, AstraZeneca) became the standard of care several years ago for patients with advanced lung cancer who have *EGFR* mutations, but less than 5% of Indian patients can afford it. In the laboratory of our colleague Dr Amit Dutt, we found that a dosing of osimertinib once a week in mice was sufficient to prevent homing of cancer cells to the mice lungs. We used that data to prescribe osimertinib once or twice a week on a compassionate basis to some of our patients who were unable to afford anything else and had no access to any other therapy, and we found that it was effective. The bottom line is that the optimal dosing of these new medicines cannot be decided by age-old methods. The traditional way of dosing has to change for antibodies, oral TKIs, and immunotherapy. For most of our modern drugs, we need to change the way we do our studies and establish the actual dosing criteria to find the optimal biological dose.

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Suggested Readings

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