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Therapeutic Role and Toxicity Profile of High-Dose Interleukin-2 in Metastatic Melanoma and Renal Cell Carcinoma: A Narrative Review.

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ABSTRACT

Background: High-dose interleukin-2 (HD IL-2) is one of the earliest clinically proven immunotherapy approaches for solid tumors. In a select subset of patients with stage III or IV metastatic melanoma and renal cell carcinoma, HD IL-2 has demonstrated the ability to induce significant and long-lasting therapeutic benefits, including durable remissions achieved without the need for further systemic treatment.

Biological Rationale: For HD IL-2 to produce durable therapeutic benefit, it must elicit a robust immune response through marked proliferation and functional activation of immune effector cells, particularly cytotoxic T lymphocytes and natural killer cells. These immune mechanisms underpin the immune-mediated tumor regression observed in responsive patients.

Clinical Efficacy: Experience from early National Cancer Institute clinical trials, as well as subsequent multi-institutional and registry-based studies, has established objective response rates of approximately 15–20% in metastatic melanoma and 20–25% in metastatic renal cell carcinoma. A small but clinically significant minority of patients achieved durable complete remissions. Those attaining complete responses have demonstrated prolonged progression-free and overall survival extending many years beyond completion of HD IL-2 therapy, often without additional treatment.

Toxicity and Limitations: The clinical use of HD IL-2 is constrained by its narrow therapeutic window and significant toxicity profile. Major adverse effects include capillary leak syndrome, cardiovascular instability, renal impairment, and neuropsychiatric toxicity. These risks necessitate inpatient administration, intensive monitoring, and restriction of therapy to highly specialized centers with appropriate expertise.

Conclusion: This narrative review evaluates the biological rationale, therapeutic efficacy, toxicity profile, and current clinical relevance of HD IL-2. Its role is contextualized within contemporary treatment paradigms dominated by immune checkpoint inhibitors and emerging engineered IL-2 variants, highlighting HD IL-2's enduring significance as a therapy capable of inducing durable, treatment-free remissions in carefully selected patients.

Keywords: *High-dose interleukin-2; Immunotherapy; Metastatic melanoma; Renal cell carcinoma; Cytokine therapy; Immune-mediated tumor response; Capillary leak syndrome; Durable remission; Immune checkpoint inhibitors; Engineered IL-2 variants.*

INTRODUCTION

Interleukin 2 (IL-2), a cytokine that serves many different functions, plays a central role in regulating adaptive immune processes such as proliferation and survival of T lymphocytes upon activation by antigens, as well as their functional maturation. CD4+ helper T cells produce IL-2 after an antigenic stimulus, which stimulates the proliferation of CD8+ T lymphocytes and NK (natural killer) cells and works to establish immunological memory. Because of these biologic activities, IL-2 was one of the first immune mediators to be utilized for systemic cancer treatment long before the advent of immune checkpoint blockade.

High dose IL-2 entered clinical development because of a series of seminal studies performed at the National Cancer Institute demonstrating reproducible immune-mediated tumor regression through the use of systemic IL-2 in a subset of patients with metastatic cancer. The consistent objective responses seen during this time along with the observation of prolonged survival among complete responders provided the rationale for the first immunotherapeutic agent to receive a formal approval from the US Food and Drug Administration, when it was approved for the treatment of metastatic renal cell carcinoma in 1992, followed by the second approval for the treatment of metastatic melanoma in 1998. This represented a pivotal moment in the history of cancer therapy, as it established that modulation of the immune system could serve as an effective therapeutic technique for solid tumors when other viable options for durable systemic treatment were non-existent.

The early identification of metastatic melanoma and renal cell carcinoma (RCC) as particularly responsive to immunotherapy with IL-2 is a product of their intrinsic properties related to tumor immunogenicity. In the case of melanoma, the tumor has a high somatic mutational burden, which translates into the generation of numerous neoantigens that will ultimately lead to the immune recognition of the tumor. Conversely, RCC has a highly vascularized and cytokine dependent local microenvironment. The existence of this type of environment would theoretically support the infiltration and activation of effector immune cells into the RCC microenvironment. As such, the above-described biological characteristics of melanoma and RCC provide a mechanistic explanation for their relative sensitivity to cytokine-based methods of enhancing the immune response.

While high-dose IL-2 has been a major contributor to the development of cancer immunotherapy, it has always been limited by its toxicity. The systemic exposure to the cytokine results in predictable but potentially life-threatening toxicities, including capillary leak syndrome, cardiovascular instability, renal impairment and neuropsychiatric effects. To safely administer this type of therapy, patients must be hospitalized in specialized centers, and the selection of eligible patients must be restricted to those who have adequate cardiopulmonary and metabolic reserves. Thus, in the current era of oncology, the dilemma between the potential for durable and treatment-free remission and the potential for life-threatening toxicities continues to be the primary consideration affecting the clinical utilization of high-dose IL-2.

METHODOLOGY

To identify studies contributing to this review, databases of academic and clinical literature were searched using PubMed, Embase and the Cochrane Library as the major sources of information due to their extensive indexing of oncology and immunotherapy literature and their validity as a source of key literature regarding the clinical development of high-dose Interleukin-2 from 1990 - December 2025.

The following categories of literature were evaluated for eligibility for inclusion in this study; clinical trials (Phase I - III), large prospective and retrospective cohorts, both national and international registries, landmark translational studies evaluating high-dose IL-2 for metastatic melanoma and renal cell carcinoma, including efficacy, durability of response, survival outcomes and toxicities related to the use of IL-2. Case reports, small series from single institutions and non-peer

reviewed sources were excluded unless they offered valuable historical or novel insight into the use of IL-2. Greater importance was placed on the interpretation of the results from primary clinical trials, while contemporary consensus reviews were used selectively to round out findings and to provide context for clinical and therapeutic developments regarding the use of IL-2.

Unlike a systematic review, this paper presents information in a narrative format and therefore is subject to selection bias. However, this narrative approach provides the opportunity to combine mechanistic, clinical, and historical elements that contribute to an overall understanding of how IL-2–based immunotherapy will continue to be seen and utilized clinically.

Ethical AI Use Disclosure Statement

The author declares that he used AI-Assisted tools in the writing and editing of this manuscript. However, the author takes full responsibility for all scientific content, including assessment of the literature, interpretation of findings, as well as providing editorial input to the paper. The author did not use AI Systems to produce original scientific conclusions, to interpret clinical data or to analyze scientific data.

IMMUNOLOGICAL BASIS OF IL-2 THERAPY

IL-2 Biology

Interleukin-2 or IL-2 mediates its effects on the immune system through a complex of proteins that are called the IL-2 receptor. This receptor consists of three different proteins - CD25 (the IL-2R alpha chain), CD122 (the IL-2R beta chain) and CD132 (the common gamma chain). Each of these chains is present on a different type of immune cell and is involved in the growth and development of that specific cell type. Activated effector T lymphocyte cells will express the high-affinity form of the receptor complex, while NK cells and memory T cells will typically express the intermediate affinity form of the receptor. Because of this heterogeneity in the receptor molecules, IL-2 has different effects at different dosages and on different types of immune cells.

Binding of the ligand to the receptor triggers intracellular signal transduction events through the actions of Janus Kinases 1 and 3 (JAK1 and JAK3), leading to phosphorylation and translocating STAT5 to the nucleus of the cell. Once the STAT pathway has been activated, the process of gene transcription begins within the nucleus and is responsible for the signals that regulate the progression of the cell cycle, cell survival, and effector cell differentiation. Simultaneously, through activation of the PI3k-AKT pathway, enhanced metabolic function and resistance to apoptosis is achieved, while through the MAPK pathway, further proliferation of effector cell expansion occurs. These multiple signal transduction pathways work collectively to produce large numbers of effector immune cells capable of producing cytotoxic effects against potentially harmful tumors.

The ability for IL-2 to stimulate not only the effector cells but also regulatory T cells, which express a high-affinity receptor for IL-2, shows that regulatory T cells can expand at the expense of effector activation, or vice versa, due in part, to the fact that regulatory T cells also express the high-affinity receptor. This explains some of the limitations in therapy with IL-2 and helps provide the rationale for designing engineered IL-2 variants that selectively stimulate effector cells and have the potential to limit the expansion of regulatory T-cells.

Mechanisms of Antitumor Activity

High-dose IL-2 helps to keep cytotoxic CD8 T cells growing and building their capabilities. Cytotoxic CD8 T cells that are growing and building their capabilities have an increased capability to recognize and kill tumors, and they produce larger amounts of pro-inflammatory cytokines that modify the tumor microenvironment and enhance the ability for the immune system to eliminate tumors.

In addition to benefiting adaptive immunity, IL-2 also enhances innate immunity by promoting the growth and activation of natural killer (NK) T cells. NK T cells do not rely solely on specific antigens to exert destruction. Natural killer T cells assist in providing additional immune surveillance in the presence of heterogeneous tumor cells. The combined activation of both adaptive and innate immune systems creates a broader opportunity for IL-2 to restore immune responses and reduce or eliminate the ability of cells to escape the immune cells based on continued loss of antigens.

A clinical finding of high-dose IL-2 treatment is that patients may attain long-term, durable complete remissions. For patients who achieve long-term disease control, the continued immune response is believed to create a stable population of tumor-specific memory T cells that can be reactivated when the patient is again exposed to tumor antigens. Therefore, the potential continued long-term overall survival associated with the use of IL-2 results from the immunologic memory created by administration of IL-2 compared to most modern-day systemic agents and provides a rationale for its continued clinical use.

HIGH-DOSE IL-2: THERAPEUTIC PROTOCOLS

Definition and Dosing Strategy

High-dose IL-2 (interleukin-2) therapy includes the administration of high enough levels of IL-2 to stimulate a strong response from the entire immune system. In terms of modern-day clinical practice, the typical method used today is to give high doses of IL-2 through intermittent intravenous bolus doses rather than giving a continuous infusion of low-dose IL-2. Standard dosing regimens typically include a dose range of 600,000 to 720,000 international units of IL-2 per kilogram body weight every eight hours, with a maximum of fourteen doses permitted during each inactive treatment cycle, depending on the patient's individual tolerance. Typically, patients receive two inactive treatment cycles with a short break in between to allow the patient to recover from acute adverse effects of the therapy.

Because of the intense physiological changes caused by the administration of IL-2, physicians will only administer this therapy to patients who are hospitalized and will require constant monitoring of hemodynamic parameters, fluid balance, cardiopulmonary function, and serial blood and urinalysis laboratory-test evaluations of renal and liver-function tests, electrolytes, and blood counts throughout their treatment. Patients receiving IL-2 therapy will be given a dose of IL-2 based on close dynamic evaluations of the patient, rather than just completing a previously established dosing schedule; in addition, any patient experiencing significant toxicity will have their IL-2 therapy interrupted early.

Patient Selection and Eligibility Criteria

The safe administration of high-dose IL-2 depends heavily on thorough patient selection. Typically, patients must have a baseline performance status of 0 or 1 (ECOG) that indicates excellent functional capacity, which represents all of the cardiopulmonary and metabolic requirements of high-dose IL-2 therapy and requires sufficient physiological reserve for tolerating transient multi-organ stress due to therapy.

All patients will go through an extensive pretreatment work-up. Cardiovascular integrity needs to be thoroughly assessed because IL-2 induces hypotension, tachyarrhythmias, and transient myocardial dysfunction in a large percentage of patients. Consequently, any patient with underlying ischemic heart disease, an impaired cardiac reserve, or significant arrhythmias will not qualify.

In addition, both adequate renal and hepatic functions are required prior to initiating therapy because the cytokine-induced capillary leak syndrome, which occurs in most patients receiving cytokines and results in multiple organ failures due to cytokine-related hypoperfusion, can lead to significant morbidity when these organs are not able to adequately respond to treatment. Pulmonary reserve is also evaluated to minimize the potential for respiratory problems associated with fluid shifts.

Individuals with active infections, poorly controlled autoimmune diseases, symptomatic CNS metastases, and significant baseline organ impairment are not candidates for high-dose IL-2 therapy. While these eligibility criteria greatly limit the number of patients eligible for treatment, they are essential to ensuring treatment-related morbidities are minimized and that the risks and benefits remain favorable for long-term responders.

CLINICAL EFFICACY

Metastatic Melanoma

High-dose interleukin-2 (IL-2) was originally investigated for the treatment of metastatic melanoma by the NCI (National Cancer Institute) and has been further developed through multiple clinical trials with additional centers. In these pivotal trials, as well as in registry trials, the rate of objective response rates has been reported to fall between 15% and 20%, indicating that IL-2 can induce an immune response to stone blasting tumor cells, even when those tumors are advanced or resistant to standard treatments. While complete responses are generally uncommon, they can present the most significant clinical change because of using IL-2.

The percentage of patients who have complete responses is approximately 5% to 8% following treatment with IL-2. In fact, studies have demonstrated that long-term follow-up in complete responders may result in lasting complete remission even years after administration of a dose of IL-2 has been stopped. The experience gained from the use of cytotoxic chemotherapy indicates that most patients experience only a short-term period of disease stabilisation before the remittance of disease re-occurs; therefore, IL-2 possesses the potential to provoke a long-term immune-mediated cure for some patients who have received it.

Data gathered from several landmark studies indicate that among complete responders, there may be a plateau effect regarding survival because of being treated with IL-2, suggesting that for a small but meaningful percentage of patients who achieve complete remission following the administration of IL-2, a functional cure may be achievable.

Metastatic Renal Cell Carcinoma

The product of the cytokine interleukin-2 has demonstrated the clinically significant activity in the treatment of advanced carcinoma associated with the kidney (metastatic renal cell carcinoma (mRCC)). Specifically, the use of IL-2 in the treatment of mRCC has been associated with improved overall response rates (20% to 25%), a significant number of patients achieving a complete response (5% to 10%).

Non-clear-cell renal cell carcinoma (NCC-RCC) has been shown to be relatively more resistant to IL-2 treatment compared to clear-cell renal cell carcinoma (CC-RCC). Histological subtype is critical when predicting IL-2 therapeutic efficacy. When comparing IL-2 treatment to other systemic therapies for mRCC and melanoma, both melanoma and RCC patients have shown a high degree of durable complete response (DCR) following IL-2 treatment; Long-term DCR is common among RCC patients who achieve a complete response after treatment with IL-2.

Additionally, these Long-term DCR demonstrate the immune-mediated response to treatment with IL-2 compared to most current systemic therapeutic agents to treat mRCC. Therefore, treatments with IL-2 should continue to be selectively incorporated within clinical practice when considering the possibilities of immune-response treatment of RCC.

Predictors of Response

Researchers attempting to identify which patients are most likely to respond favorably to high-dose IL-2 have evaluated both clinical and immunologic factors. Favorable clinical factors include patients with less tumor burden overall, better functional capabilities, and no large volume number of visceral metastases. It is believed that these factors may represent a less immunosuppressive tumor microenvironment as well as being more amenable to amplification of the immune response.

Investigational studies examining biomarkers indicate that patients who have higher lymphocyte counts prior to starting therapy, as well as having a higher density of immune cells that are infiltrating into their tumors and have evidence of having an immune response to their cancer prior to treatment, may have improved response rates. Despite some promise for these findings, none of these associations is universally established from patient study to patient study, and thus no clinically validated predictive method for selecting appropriate patients has been created. Thus far, patient selection primarily depends upon the clinical judgment of the investigator regarding the performance status of the patient, the organs involved, and their overall distribution of disease.

TOXICITY PROFILE OF HIGH-DOSE IL-2

The use of high-dose interleukin-2 (IL-2) can be associated with an acute toxicity syndrome characterized by the activation of the immune system, and that endothelial cell dysfunction, due to cytokine-induced endothelial cell activation; the toxic effect of this syndrome is markedly dose-dependent. There will be some reversibility of most effects with adequate supportive care; however, due to the severity of the effects, the administration of high-dose IL-2 requires administration and monitoring in a specialized inpatient setting for constant monitoring and rapid practice of intervention.

Capillary Leak Syndrome

Capillary Leak Syndrome is the defining toxicity and primary toxicity associated with high-dose IL-2 treatment. Cytokines cause activation of endothelial cells, which results in increased permeability of the blood vessels, leading to the passage of fluid and protein from the vascular space to the extravascular space. Patients experience the following clinical signs: dehydration; accumulation of fluid in the body compartments; decreased urine volume; and increased hematocrit and hemoglobin concentration in the blood. The severity of Capillary Leak Syndrome typically increases with the cumulative dose of high-dose IL-2 within each treatment cycle and is managed by closely monitoring hemodynamics; judicious use of intravenous fluids; and the timely initiation of vasopressors when indicated. The management of Capillary Leak Syndrome may lead to interruptions or discontinuations in the delivery of high-dose IL-2 based on clinical severity rather than on where the patient is on a pre-designed dosing schedule.

Cardiopulmonary Toxicity

A common complication of IL-2 therapy is hemodynamic instability, which is also a major limiting factor for dosing. Hypotension is often seen requiring medication assistance to maintain blood pressure, and patients may experience temporary heart rhythm irregularities (both supraventricular and ventricular arrhythmias), necessitating continuous monitoring with an electrocardiogram.

The primary cause of pulmonary toxicity is the presence of interstitial and alveolar fluid as a result of capillary leak syndrome. Patients presenting with pulmonary congestion will often have trouble breathing, low oxygen saturation in the blood, and may show changes on chest radiographs. In addition to initiating supplemental oxygen therapy, other management strategies include careful fluid administration, a temporary pause in IL-2 therapy until the patient's respiratory function stabilizes, and the use of appropriate medications.

Renal, Hepatic, and Neurological Effects

Renal dysfunction seen with IL-2 therapy is often attributed to reduced blood flow to the kidneys related to the effects of cytokines rather than from direct damage caused by IL-2. Acute kidney injury may result in oliguria and increasing serum creatinine levels, and it is generally reversible once hemodynamic stability is restored, and the administration of IL-2 is ceased. A common effect of therapy resulting from IL-2 is temporary elevation of hepatic transaminases and bilirubin levels, due to an inflammatory response in the liver. Normally, these laboratory abnormal findings will resolve spontaneously once treatment is completed.

Lastly, an array of neurological effects can occur while receiving IL-2; these include mild cognitive slowing and mood changes to more severe presentations of agitation, confusion, or hallucinations. Neurological complications are believed to result from the systemic immunity response to IL-2 therapy as well as metabolic changes associated with the treatment that can alter blood flow to the brain. A prompt neurological evaluation should be performed on any patient experiencing severe neurotoxicity from therapy.

Treatment-Related Mortality and Risk Mitigation

Historically, high-dose IL-2 (interleukin-2) was associated with significant mortality due to treatment-related complications. However, the development of more defined patient eligibility criteria, standardization of toxicity management clinical pathways, and the implementation of multidisciplinary teams providing supportive care have led to a decreased incidence of fatal complications related to treatment with IL-2. Current practice involves using only experienced medical centers with direct access to intensive medical support services when administering high-dose IL-2 for cancer therapy. Therefore, strict eligibility criteria must be adhered to, as well as continuous monitoring and interventions early on that are supportive of patients to decrease the risk of treatment-related complications.

COMPARISON WITH MODERN IMMUNOTHERAPIES

Conceptual and Mechanistic Distinctions

The unique immunological treatment paradigms offered through high-dose IL-2 and immune checkpoint inhibitors have many differences in their mechanisms of action as well as the effects they produce through those mechanisms. The action of IL-2 is to directly increase the number of immune effector cells by rapidly expanding the number of lymphocytes and natural killer cells. More specifically, these immune effector cells (NK) are rapidly produced, resulting in rapid proliferation and activation of the immune effector cell (NK) population. In turn, this rapid proliferation and activation results in widespread systemic immune stimulation over short periods of time. Conversely, checkpoint inhibitors indirectly enhance the ability of the immune response to fight cancer by removing the inhibitory signals associated with the immune response.

Those mechanistic differences lead to markedly different clinical profiles. Checkpoint inhibitors have significantly higher overall response rates in diverse patient populations, and they have become standard of care for patients with metastatic melanoma and renal cell carcinoma. However, durable disease control with checkpoint inhibitors generally requires continued treatment. Although there is a lower overall frequency of response to high-dose IL-2, it is still unique in that the subset of patients who are selected for treatment with this modality are likely to have long-lasting durable remissions that do not require continued treatment following the initiation of therapy.

Balancing Therapeutic Benefit and Toxicity

Compared to current checkpoint-based therapies, the high-dose IL-2 risk-to-reward ratio is extremely different. The risks associated with use of high-dose IL-2 include intense, predictable, and primarily reversible side effects which must be treated in the hospital and should be limited to patients who have good physiologic reserves to endure them. Conversely, patients receiving checkpoint inhibitor therapies are usually given treatment outside of a hospital setting. Therefore, checkpoint inhibitors are generally much more acceptable and broader in the number of patients able to use them, although, like IL-2, may have life-threatening immune-related reactions that may occur unpredictably.

Checkpoint inhibitor therapy's high tolerability and wide-spread acceptability when compared to IL-2 has promoted more frequent use in day-to-day medical practices. However, the fact that CTLA-4 and anti-PD1 monoclonal antibodies induce durable complete remissions is yet another distinction that sets high-dose IL-2 apart both biologically and clinically from most of the contemporary agents currently being used.

Combination and Sequential Strategies

A growing body of research suggests that combining or sequencing the use of IL-2 and immune checkpoint inhibitors may be a useful strategy to improve clinical outcomes. Checkpoint inhibitors are thought to increase the size of the pool of lymphocytes that respond to tumors, while IL-2 enhances the activity of those same lymphocytes through its stimulating effect. In contrast, IL-2 can also enhance the duration of responses initially induced by checkpoint inhibitors. Although researchers have been somewhat cautious about examining how different combinations of the two therapies might impact the risk of added toxicity, recent studies indicate that new engineered IL-2 variants that preferentially stimulate lymphocytes preferred for the immune response while minimizing systemic toxicity may provide an effective approach to limit potential adverse events. Furthermore, combining therapies using a sequence in which an IL-2 injection is given after initial node involvement with checkpoint inhibitors shows that responses remain active when these therapies are combined and may remain viable as newer medicines are developed.

CURRENT ROLE AND CLINICAL RELEVANCE

Enduring Clinical Significance

Immune checkpoint inhibitors and targeted therapies are the dominant treatment in the current treatment algorithms for metastatic melanoma and renal cell carcinoma; however, high-dose interleukin-2 (IL-2) is still a unique clinical entity. The long-term clinical significance of IL-2 is its ability to induce long-term complete responses in a small group of patients without the need for further treatment, a happening that is rare for even the newest immunotherapy drugs. As the only immunotherapy drug with this biologic difference, IL-2 provides both conceptual and clinical value, even though the everyday use of IL-2 is decreasing.

In addition to providing clinical value, the long-term follow-up of patients treated with IL-2 gives clinicians unique insight into the natural history of responsive immune-mediated tumor eradication; therefore, the data from long-term follow-up have provided the foundation of developing and evaluating new immunotherapeutic approaches to achieve durable anticancer immunity.

Selective Use and Niche Applications

Currently, clinicians utilize high doses of Interleukin-2 (IL-2) only for those patients whose organ function is intact, whose overall condition is G (good), and where IL-2 has been found to be potentially curative due to the type of cancer(s) involved (e.g. clear cell renal cell carcinoma and specific subtypes of melanoma).

However, due to the need for specialized infrastructure within the institutions administering IL-2 as well as experienced multidisciplinary teams to support its safe delivery, the use of IL-2 is limited to only a few specialized centers across the United States (U.S.). At these specialized treatment facilities, patients with tumors that potentially respond to IL-2 are offered this treatment on the basis that they are willing to accept the risks associated with the use of IL-2 for the potential of longer-term tumor control.

Economic and Resource Considerations

High doses of IL-2 lead to many upfront resource expenditures for hospitalization, intensive monitoring, and supportive care. However, patients who achieve durable remission will not need systemic therapy for the duration of the life of that patient, thus leading to long-term economic savings versus treating patients with drug regimens of chronic nature. These financial aspects clearly provide a rationale for using IL-2 selectively in patients who have a high probability of receiving a substantial benefit.

FUTURE DIRECTIONS

Development of Modified IL-2 Therapeutics

The very high levels of toxicity associated with IL-2 administered at high doses has led to the development of engineered IL-2 molecules specifically designed to allow for an increased therapeutic window. The altered IL-2 drugs are made to preferentially stimulate antitumor effectors and provide less stimulation of regulatory T-cells and endothelial cells (i.e., increasing the risk of capillary toxicity and systemic effects associated with vascular endothelium) than the conventional IL-2. The methods of engineering these IL-2 variants include, but are not limited to, altering the receptor binding profile of IL-2, pegylation of IL-2, fusion protein constructs of IL-2, and targeted delivery platforms for IL-2.

Initial investigations of these engineered IL-2 variants suggest that it may be possible to take advantage of the positive effects of immune amplification generated by IL-2, with reduced systemic toxicities and side effects than would have been experienced through conventional IL-2 administration. If the initial studies can be further validated in larger clinical trials, it is expected that engineered IL-2 variants will become broadly used for the treatment of patients and be used in conjunction with other Immunotherapeutics in practice today.

Combined and Sequential Immunotherapy Strategies

Combining IL-2-based therapy with immune checkpoint inhibitors is an active area of clinical investigation, as these agents may enhance the antitumor response to checkpoint blockade in patients who have responded partially or transiently to the latter therapy by enhancing the proliferation of lymphocytes and their functional capacity. On the other hand, by preparing the immune environment for the actions of IL-2, checkpoint blockade may create more effective conditions under which IL-2 can expand and enhance the proliferation of T cells.

Currently, many clinical trials are being conducted to find out how best to sequence IL-2 treatment and immune checkpoint blockade, determine appropriate dosages of both treatments, and mitigate the risk of increased immune-related adverse events (irAE) due to excessive immune stimulation by both treatments. These clinical trials demonstrate the shift to a comprehensive approach toward rationally designed combination Immunotherapeutics based on the mechanistic complementarity of these two therapeutic classes.

Toward Personalized Immune-Based Therapy

With advances made in immune profiling and biomarker development, we will be able to better personalize IL-2 treatments. By looking at the immune environment around the tumor, specifically the balance between effector and regulatory lymphocytes, patterns of cytokine signaling, and expression levels of immune checkpoints, we will be able to identify the best candidates for long-term benefit from IL-2-induced immune amplification.
Using molecular and immunologic biomarkers will allow us to better select patients who would benefit from treatment while minimizing unnecessary treatment of low probability candidates and maximizing the benefit of treatments through better selection processes. As the field of precision oncology continues to grow and evolve, we may see a resurgence of IL-2 therapies that are more sophisticated and targeted than previously used.

LIMITATIONS OF EXISTING EVIDENCE

Absence of Contemporary Comparative Trials

Evaluating the use of high-dose interleukin-2 has a significant drawback because there are no randomized clinical trials conducted in the current era of immunotherapy. The efficacy and safety data for the product have been developed before the development of immune checkpoint inhibitors and targeted therapies became widely used, thereby precluding a direct comparison with current standard of care therapies. As a result, relative assessments of the therapeutic value of IL-2 are based largely on historical data rather than current head-to-head comparative clinical evidence.

Impact of Selective Patient Enrollment

The unique and very structured recruitment process used in clinical trials of IL-2 has a substantial impact on the outcome for each patient. In addition to safety for those who receive study treatment, this type of recruitment creates a bias in the way that potential patients are chosen. As a result, the likely success of IL-2 may not be representative of what can be achieved in the general oncology patient population; rather, this selective enrollment creates an inflated view of the likely success rate of IL-2 and a diminished representation of the potential risks of IL-2 treatment in a more expansive oncology population.

Constraints on External Validity

High-dose IL-2 is prescribed in institutional settings that have been developed specifically to employ high-dose IL-2. Each institution may create its own unique protocols, toxicity management plans, and patient follow-up procedures, thereby providing a very different experience than what would occur if the same treatment were to be provided to an individual patient outside of an institutional setting. Because of this variability, the results of existing clinical trials may not necessarily be applicable to routine oncology clinical practice.

CONCLUSION

High-dose IL-2 is a unique milestone in the history of developing cancer immunotherapies. It was among the very first systemic therapies to illustrate the potential of immune modulation to elicit durable, treatment-free remissions in patients with metastatic melanoma and renal cell carcinoma. High-dose IL-2 has a low overall response rate but produces profound and lasting benefits in a subset of patients, making it one of the most dramatic and unprecedented drugs from both a clinical and biological standpoint.

Due to the limited therapeutic window and high toxicity associated with high-dose IL-2, only carefully selected patients can receive this treatment, and it must be administered in specialized treatment settings. The emergence of immune checkpoint inhibitors has largely replaced IL-2 in the first-line treatment setting as they can be used more broadly, are better tolerated, and are therefore increasingly used in today's cancer patients. Nevertheless, due to the inherent ability of high-dose IL-2 to create long-lasting complete remissions without continuous treatment, it is still in a unique position compared to most of the other drugs currently available.

In today’s environment of utilizing immunotherapy to treat cancer, high-dose IL-2 has transitioned from a commonly applied treatment to one that is increasingly being used more selectively and as a niche treatment for a selected population of patients. However, the fact that high-dose IL-2 is still being utilized is relevant to the development of other new immunotherapies based on the knowledge gained from high-dose IL-2. As the field continues to advance, it is likely that therapies that utilize IL-2 will once again find their way to the clinic in forms that are consistent with the concept of precision oncology.

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