Review Article

Prospects of IL-2 in Cancer Immunotherapy

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IL-2 is a powerful immune growth factor and it plays important role in sustaining T cell response. The potential of IL-2 in expanding T cells without loss of functionality has led to its early use in cancer immunotherapy. IL-2 has been reported to induce complete and durable regressions in cancer patients but immune related adverse effects have been reported (irAE). The present review discusses the prospects of IL-2 in immunotherapy for cancer.

1. Introduction

Interleukin-2 (IL-2) was identified in the supernatants of activated T cells over three decades ago [1, 2]. IL-2 is the first cytokine for which receptor component was cloned [3, 4]. IL-2 is a four α-helical bundle cytokine of 15.5 kDa size. It is mainly produced by CD4+ T cells as a result of antigen stimulation response [5]. However, to some extent, IL-2 is also produced by NK T cells [6], CD8+ cells [7], mast cells [8], and dendritic cells (DCs) [9]. IL-2 possesses potent T cell growth factor action. It can also induce natural killer (NK) cells and potentiate their cytolytic effect and promote many other immune system components which are required for the removal of autoreactive cells and maintenance of homeostasis [10]. In the last two decades, the potential of IL-2 to expand T cells without affecting its activity has led to identification of its potential as an immunotherapeutic agent against cancer. The IL-2 administration is reported to induce apparently curative and durable regressions in cancer patients. In 1988, UFDA approved IL-2 for therapy of metastatic melanoma and then in 1992 for renal cell cancer. Further research also led to evolution of cell transfer therapies having promising response against melanoma cases [11]. This review discusses scope of IL-2 in the immunotherapy of cancer and major challenge in the development of IL-2 based therapeutic approach as well as perspective on future research.

2. IL-2 Receptor and Signaling

IL-2 is a T cell-derived common cytokine. It plays vital role in growth as well as differentiation of T cells, B cells, natural killer cells, and many other cell types [12]. The signaling pathway of IL-2 is mediated by a selective receptor family [13], which includes three classes of cell surface receptors: the alpha (α), beta (β), and gamma (γ) chains. The dimeric low affinity IL-2 receptor consists of the γ and β chains and is expressed on T cells and NK cells. The high affinity IL-2 receptor consisting of the α, β, and γ chains is expressed on Tregs and activated T cells [14, 15]. The activated lymphocytes also express these high affinity receptors. The low and high
affinity IL-2 receptors are expressed in steady state. The transcription of IL-2R is induced by various factors. Transcription of IL-2R is induced on T cells which are activated by TCR or IL-2 on T cells. Transcription of IL-2R is induced by various factors. Transcription of IL-2Rα is induced on T cells which are activated by TCR or IL-2 [16]. IL-2Rα transcription is also induced by intermediate affinity receptors upon binding of IL-2 and as a response to T cell activation. There is also rapid formation of high affinity receptors and consequent increase in responsiveness to IL-2.

Expression of IL-2Rβ chain is also induced by IL-2 on T cells [23]. These cells also have γ chain expression but it is less inducible than IL-2Rα or IL-2Rβ [24]. IL-2Rα is also expressed by NK cells, B cells, mature dendritic cells (DCs), and endothelial cells [25–28]. This binding also promotes cytolytic activity and cell growth [29].

IL-2 presented in trans and bound to cellular IL-2Rα can also activate another cell having IL-2Rβ and γ chain expression [30]. However, it should be noted that the affinity with which IL-2 can bind to IL-2Rα is relatively low with rapid on and off rates.

IL-2 binding to IL-2Rαβγ or IL-2Rβγ complex initiates signal transduction for the transcription of target genes through multiple signaling pathways. These include Janus kinase (JAK) signal transducer and activator of transcription (STAT) pathway, the phosphoinositide 3-kinase (PI3K) AKT pathway, and the mitogen-activated protein kinase (MAPK) pathway (Figure 1). All of these three major pathways mediate the effect of IL-2 on cell proliferation, activation, differentiation, survival, and cytokine production in the immune cells [31,32].

3. Cancer Immunotherapy Using IL-2

It has been long established that the immune system can be harnessed against neoplastic cells. However, IL-2 was the first cytokine to be successfully used in the treatment of cancer. This was because it can promote T cells as well as NK cells. IL-2 can induce T cell proliferation and differentiation and also cause its activation. The complexing IL-2 with anti-IL-2 mAbs has ability to potentiate signaling via the intermediate affinity CD122/CD132 receptor in vivo. Kamimura and Bevan examined the effect of treatment of naive CD8+ T cells with IL-2 signals in vivo. Extensive division was observed in T cell upon treatment of the host animals with IL-2 and anti-IL-2 complexes in the absence of any other stimulation. The potent IL-2 signals caused proliferation and differentiation of naive CD8+ T cells into functional memory cells having conventional central memory phenotype [33].

Further, lymphokine activated killer (LAK) cells represent a unique and fundamental cytotoxic effector system plays a role in immune surveillance against NK resistant solid tumor cells and has role in the adoptive immunotherapy. LAK cells are a heterogeneous mixture of ex vivo expanded and activated T, NK, and NKT cells which display major histocompatibility complex (MHC) nonrestricted cytotoxicity that do not rely on HLA-mediated recognition of tumor targets. LAK cells can recognize and kill human cancer cells as well
Promising Immunotherapy

The major challenge in the development of IL-2 as a therapeutic antitumor agent is that IL-2 can act on both T cells and Tregs. Thus, reports on use of IL-2 have used two different strategies, one to reduce the autoimmune responses and another to augment immune responses against tumor 

4. Dual Effect of IL-2: Major Challenge in the Development of Promising Immunotherapy

The major challenge in the development of IL-2 as a therapeutic antitumor agent is that IL-2 can act on both T cells and Tregs. Thus, reports on use of IL-2 have used two different strategies, one to reduce the autoimmune responses and another to augment immune responses against tumor (Table 1). Recently, studies have used IL-2 in low dose, either alone or in combination, to induce preferential activation of Tregs. Tregs having high affinity for IL-2 can compete more effectively for it at low IL-2 levels [54]. Few studies involving HCV induced vasculitis and Graft-Versus-Host Disease showed improvement in clinical outcome based on the described concept of IL-2 therapy using low doses. However, in the study involving renal cancer and melanoma, subjects which were given high dose of IL-2 showed limited efficacy due to increased Treg level [18, 22, 55]. Development of somewhat lethal toxicity is another major limitation of therapy with IL-2 at high doses. Also, IL-2 has a very short life in systemic delivery. Attempts made to reduce the side effects by lowering dose resulted in marked loss of therapeutic effect due to dominant effect of immunosuppressive Treg cell leading to poor outcomes in cancer patients [18]. Further studies are needed to explore the dual effect of IL-2 in cancer therapy. The translation of effect of IL-2 on Tregs and effector cell from preclinical to clinical setting is not always predictable [56, 57]. This is so because there are a number of factors influencing the outcome in clinical condition (e.g., genetic variability, disease factor, and most importantly the variation in Tregs and effector cells immune response in individuals). There is also an unmet need for better biomarkers which can be used to predict the response of IL-2 immunotherapy and hence can predict factors like genetic polymorphisms or serum proteins or antigen expression. This can also lead to development of a more personalized therapy approach based on the individual characteristics of patient especially the ones who are expected to benefit from IL-2 therapy.
| Treatment type | Disease condition | Treatment | Comments | Ref. |
|----------------|------------------|-----------|----------|-----|
| **High dose treatment** | Melanoma/renal cell cancer | 720,000 IU/kg of i.v. IL-2 given eight hourly (up to 15 doses per cycle) | Complete response in 7% and partial regression in 10% of metastatic melanoma patients | [17] |
| | Metastatic melanoma/renal cell carcinoma | 720,000 IU/kg of i.v. IL-2 given eight hourly (up to 15 doses per cycle) | The proportion of CD4+CD25hi T cells in total CD4 T cells showed 6-fold increase compared to pretreatment level | [18] |
| | Melanoma | IL-2 as high-dose bolus 8 hourly or gp100 single dose per cycle, along with high-dose IL-2 on the second day | The combination of interleukin-2 and gp100:209–217 (210M) peptide vaccine exhibited relatively higher response rate compared to interleukin-2 alone | [19] |
| | Renal cell carcinoma | 720,000 or 600,000 IU/kg of i.v. IL-2 given 8 hourly to a maximum of 14 doses per cycle | HD IL-2 as sole front-line therapy, in the absence of added therapy exhibited extended clinical benefit | [20] |
| **Low dose treatment** | Graft versus host disease | Low s.c. dose (300,000; 1,000,000 or 3,000,000 IU/m²) of IL-2 for eight weeks | Twelve out of the twenty three evaluated patients exhibited good responses at multiple sites. | [21] |
| | HCV-induced vasculitis | 1,500,000 IU/day of for 5 days, followed by 3 × 10⁶ IU per day of IL-2 for 5-day given at 3rd, 6th, and 9th week | The sustained clinical and Immunologic responses was observed in patients who received IL-2 for extended period | [22] |

5. Future Perspective of IL-2 Based Immunotherapy

IL-2 was one of the first cytokines exploited for development of tumor immunotherapy. However, the contrasting action of IL-2 has led to confusing response and limited the development of IL-2 for tumor immunotherapy. Further, the delivery of IL-2 has been associated with multiple side effects, further affecting its utility in clinical setting. Development of IL-5 for cancer immunotherapy was initiated in the last decade and it was viewed as a safer successor to IL-2-based immunotherapies since both cytokines have shared receptor subunits and activated similar downstream pathways. Preclinical data suggested IL-5 to be safer alternative to IL-2 immunotherapy [58]. However, translational challenges and issues in delivery affected its clinical development [58]. However, recently Nektar Therapeutics has developed a memory T cell stimulating cytokine, NKTR255, which causes long-term T cell activation through IL-15 pathway. According to the company, it has been found to improve the quality of T cell memory response to treat cancer. Through optimal engagement of the, NKTR-255 stimulates proliferation and survival of CD8+ T cells and natural killer (NK) cells through optimal engagement of IL-15Rα/IL-2Rγ receptor complex and induces long-term immunological memory for sustained antitumor immune response [59]. Recently a complex between a novel human IL-15 superagonist variant and a human IL-15Rα sushi domain-Fc fusion protein, termed ALT-803, has been created. ALT-803 showed promising immunostimulatory activity and antimyeloma activity in mouse model with relatively longer half-life than IL-15 and wide therapeutic dose range. The potent immunostimulatory activity of ALT-803 is also attributed to its prolonged retention in lymphoid organs compared to IL-15 [60, 61].

Development of better understanding of immune responses of IL-2 can open new windows for developing better immunotherapy. Many strategies are being developed to improve efficacy, while reducing the toxicity of IL-2 therapy. The recent evidence suggests that genetic variation plays an important role in defining the clinical output of immunotherapy. Some studies have identified functional polymorphism as a reason for poor response to therapies [62, 63]. Further exploration of polymorphism in IL-2 gene can help in elucidation of clinical response. Efforts have also been focused on development of mutant form of IL-2 with preferential binding to different IL-2R. This has potential to bypass interaction of IL-2 with other subtypes of receptors [64]. This strategy has been tried as part of Phase I study against cases of renal cancer and advanced melanoma [65]. Mutational approaches to construct IL-2 mutants with varying binding affinities for components of the IL-2 receptor have been tried in few reports. This includes
strategy to enhance binding to IL-2Ra chain. The objective is to improve IL-2 efficacy based on the fact that effect T cells have relatively higher expression of α chain. On the contrary, alternate strategy is to employ creation of mutants having impaired binding to β chain. This can help in reducing expression of NK cells which have higher βγ expression while retaining the property for effector T cell stimulation [66–69]. One study used IL-2 mutants having enhanced binding to β chain. The residues in the mutant IL-2 caused conformation effect in IL-2 leading to improved binding to the β chain. One of the mutants is known as “superkine” due to its enhanced agonistic effect. This superkine also exhibited relatively improved antitumor activity with relatively lesser side effects compared to systemic IL-2 therapy [70]. Improvement of half-life of IL-2 is another important aspect for improving development of effective IL-2 based immunotherapy. This can greatly reduce the dose of IL-2, while leaving a positive shift in clinical outcome [71]. Combination of IL-2 with monoclonal antibodies is also being utilized as a new approach in cancer immunotherapy. It can be used for targeted approach against specific cells based on the affinity of their IL-2R. The immunocytokines, namely, antibody–cytokine fusion proteins, have already been tested in preclinical cancer models [29]. Sockolosky et al. have recently developed engineered IL-2 cytokine-receptor orthogonal (ortho) pairs that interact with one another. This ortho IL-2 transmits native IL-2 signals but does not interact with their natural cytokine and receptor counterparts since it lacks detectable binding to IL-2. Ortho IL-2 pairs showed good efficacy as in mouse model of adoptive cell therapy [72].

IL-2 immunotherapy, being effective treatment option, is associated with various toxicities. Developing predictive biomarker can help optimize selection of appropriate patient population which is likely to be most benefited from therapy. Recently, Kuzman et al. have shown the positive relation between Neutrophil-lymphocyte ratio and toxicity from IL-2 therapy. Recently, Kuzman et al. have shown the positive relation between Neutrophil-lymphocyte ratio and toxicity from IL-2 therapy. In a recent study, Kuzman et al. [72] evaluated the Neutrophil-Lymphocyte ratio (NLR) in patients receiving IL-2 therapy and found a positive correlation between NLR and toxicity. The authors declare that they have no conflicts of interest.

**Conflicts of Interest**

The authors declare that they have no conflicts of interest.

**References**

[1] O. Boyman and J. Sprent, “The role of interleukin-2 during homeostasis and activation of the immune system,” *Nature Reviews Immunology*, vol. 12, no. 3, pp. 180–190, 2012.

[2] T. Waldmann, Y. Tagaya, and R. Bamford, “Interleukin-2, interleukin-15, and their receptors,” *International Reviews of Immunology*, vol. 16, no. 3–4, pp. 205–226, 1998.

[3] T. Taniguchi, H. Matsui, T. Fujita et al., “Structure and expression of a cloned cDNA for human interleukin-2,” *Nature*, vol. 302, no. 5906, pp. 305–310, 1983.

[4] T. Nikaido, A. Shimizu, N. Ishida et al., “Molecular cloning of cDNA encoding human interleukin-2 receptor,” *Nature*, vol. 311, no. 5987, pp. 631–635, 1984.

[5] W. J. Leonard, “Cytokines and immunodeficiency diseases,” *Nature Reviews Immunology*, vol. 1, no. 3, pp. 200–208, 2001.

[6] M. A. Yui, L. L. Sharp, W. L. Havran, and E. V. Rothenberg, “Preferential activation of an IL-2 regulatory sequence transgene in TCRαβ and NKT cells: subset-specific differences in IL-2 regulation,” *The Journal of Immunology*, vol. 172, no. 8, pp. 4691–4699, 2004.

[7] X. Paliard, R. de Waal, H. Malefijt et al., “Simultaneous production of IL-2, IL-4, and IFN-γ by activated human CD4+ and CD8+ T cell clones,” *The Journal of Immunology*, vol. 141, no. 3, pp. 849–855, 1988.

[8] A. Y. Hershko, R. Suzuki, N. Charles et al., “Mast cell interleukin-2 production contributes to suppression of chronic allergic dermatitis,” *Immunity*, vol. 35, no. 4, pp. 562–571, 2011.

[9] F. Granucci, C. Vizzardelli, N. Pavelka et al., “Inducible IL-2 production by dendritic cells revealed by global gene expression analysis,” *Nature Immunology*, vol. 2, no. 9, pp. 882–888, 2001.

[10] C. C. Almanca, S. V. Saldanha, D. R. Sousa et al., “Toxicological evaluation of acute and sub-chronic ingestion of hydroalcoholic extract of *Solanum cernuum* Vell. in mice,” *Journal of Ethnopharmacology*, vol. 138, no. 2, pp. 508–512, 2011.

[11] S. A. Rosenberg, “IL-2: the first effective immunotherapy for human cancer,” *The Journal of Immunology*, vol. 192, no. 12, pp. 5451–5458, 2014.

[12] N. A. Cacalano and J. A. Johnston, “Interleukin-2 signaling and inherited immunodeficiency,” *American Journal of Human Genetics*, vol. 65, no. 2, pp. 287–293, 1999.

[13] R. J. Robb, A. Munck, and K. A. Smith, “T cell growth factor receptors: Quantitation, specificity, and biological relevance,” *The Journal of Experimental Medicine*, vol. 154, no. 5, pp. 1455–1474, 1981.

[14] D. J. Stauber, E. W. Dehler, P. A. Horton, K. A. Smith, and I. A. Wilson, “Crystal structure of the IL-2 signaling complex: Paradigm for a heterotrimeric cytokine receptor,” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 103, no. 8, pp. 2788–2793, 2006.

[15] X. Wang, M. Rickert, and K. C. Garcia, “Structural biology: Structure of the quaternary complex of interleukin-2 with its α, β and γc receptors,” *Science*, vol. 310, no. 5751, pp. 1159–1163, 2005.

[16] J. M. Depper, W. J. Leonard, C. Drogula, M. Krönke, T. A. Waldmann, and W. C. Greene, “Interleukin 2 (IL-2) augments transcription of the IL-2 receptor gene,” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 82, no. 12, pp. 4230–4234, 1985.

[17] S. A. Rosenberg, J. C. Yang, S. L. Topalian et al., “Treatment of 283 consecutive patients with metastatic melanoma or renal
cell cancer using high-dose bolus interleukin 2," *Journal of the American Medical Association*, vol. 271, no. 12, pp. 907–913, 1994.

[18] M. Ahmazadeh and S. A. Rosenberg, "IL-2 administration increases CD4+CD25hi Foxp3 + regulatory T cells in cancer patients," *Blood*, vol. 107, no. 6, pp. 2409–2414, 2006.

[19] D. J. Schwartzentruber, D. H. Lawson, J. M. Richards et al., "gp100 peptide vaccine and interleukin-2 in patients with advanced melanoma," *The New England Journal of Medicine*, vol. 364, no. 22, pp. 2199–2207, 2011.

[20] J. L. Clark, M. K. K. Wong, H. L. Kaufman et al., "Impact of sequencing targeted therapies with high-dose interleukin-2 immunotherapy: an analysis of outcome and survival of patients with metastatic renal cell carcinoma from an on-going Observational IL-2 clinical trial: PROCLAIMSM," *Clinical Gastrointestinal Cancer*, vol. 15, no. 1, pp. 31–41.e4, 2017.

[21] J. Loreth, K. Matsuoka, H. T. Kim et al., "Interleukin-2 and regulatory T cells in graft-versus-host disease," *The New England Journal of Medicine*, vol. 365, no. 22, pp. 2055–2066, 2011.

[22] D. Saadoun, M. Rosenzweig, F. Joly et al., "Regulatory T-cell responses to low-dose interleukin-2 in HCV-induced vasculitis," *The New England Journal of Medicine*, vol. 365, no. 22, pp. 2067–2077, 2011.

[23] J. P. Siegel, M. Sharon, P. L. Smith, and W. J. Leonard, "The IL-2 receptor β chain (p70): Role in mediating signals for LAK, NK, and proliferative activities," *Science*, vol. 238, no. 4823, pp. 75–78, 1987.

[24] X. Cao, C. A. Kozak, Y. J. Liu, M. Noguchi, E. O'Connell, X. Zhang, S. Sun, I. Hwang, D. F. Tough, and J. Sprent, "Potent effects of IL-2 in mice: evidence for IL-2 receptor complexes in vivo," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 90, no. 18, pp. 8464–8468, 1993.

[25] M. Brisslert, M. Bokarewa, P. Larsson, K. Wing, L. V. Collins, and A. Tarkowski, "Phenotypic and functional characterization of human CD25+ B cells," *The Journal of Immunology*, vol. 167, no. 4, pp. 548–557, 2006.

[26] C. Wiest, S. Létourneau, G. Pantaleo, and O. Boyman, "Improved IL-2 immunotherapy by selective stimulation of IL-2 receptors on lymphocytes and endothelial cells," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 107, no. 26, pp. 11906–11911, 2010.

[27] A. Y. Rudensky, "Regulatory T cells and Foxp3," *ImmunoReviews*, vol. 241, no. 1, pp. 260–268, 2011.

[28] X. Zhang, S. Sun, I. Hwang, D. F. Tough, and J. Sprent, "Potent and selective stimulation of memory-phenotype CD8+ T cells in vivo by IL-15," *Immunity*, vol. 8, no. 5, pp. 591–599, 1998.

[29] W. Liao, J. -X. Lin, and W. J. Leonard, "Interleukin-2 at the crossroads of effector responses, tolerance, and immunotherapy," *Immunity*, vol. 38, no. 1, pp. 13–25, 2013.

[30] S. C. Wuest, J. H. Edwan, J. F. Martin et al., "A role for interleukin-2 trans-presentation in dendritic cell-mediated T cell activation in humans, as revealed by dacilizumab treatment," *Nature Medicine*, vol. 17, no. 5, pp. 604–609, 2011.

[31] M. Rickert, X. Wang, M. J. Boulanger, N. Goriatcheva, and K. C. Garcia, "Structural Biology: The structure of interleukin-2 complexed with its alpha receptor," *Science*, vol. 308, no. 5727, pp. 1477–1480, 2005.

[32] G. C. Sim and L. Radvanyi, "The IL-2 cytokine family in cancer immunotherapy," *Cytokine & Growth Factor Reviews*, vol. 25, no. 4, pp. 377–390, 2014.

[33] D. Kamimura and M. J. Bevan, "Naïve CD8+ T cells differentiate into protective memory-like cells after IL-2-anti-IL-2 complex treatment in vivo," *The Journal of Experimental Medicine*, vol. 204, no. 8, pp. 1803–1812, 2007.

[34] E. A. Grimm, K. M. Ramsey, A. Mazumder, D. J. Wilson, J. Y. Djeu, and S. A. Rosenberg, "Lymphokine-activated killer cell phenomenon II. Precursor phenotype is serologically distinct from peripheral T lymphocytes, memory cytotoxic thymus-derived lymphocytes, and natural killer cells," *The Journal of Experimental Medicine*, vol. 157, no. 3, pp. 884–897, 1983.

[35] S. E. Ettinghausen and S. A. Rosenberg, "Immunotherapy of murine sarcomas using lymphokine activated killer cells: optimization of the schedule and route of administration of recombinant interleukin-2," *Cancer Research*, vol. 46, no. 6, pp. 2784–2792, 1986.

[36] M. T. Lotze, B. R. Leong, D. J. Mathisen, and S. A. Rosenberg, "The in vivo distribution of autologous human and murine lymphoid cells grown in T cell growth factor (TCGF): Implications for the adoptive immunotherapy of tumors," *The Journal of Immunology*, vol. 125, no. 4, pp. 1487–1493, 1980.

[37] A. R. D. V. Chavez, W. Buchser, P. H. Basse et al., "Pharmacologic administration of interleukin-2: Inducing a systemic autophagic syndrome," *Annals of the New York Academy of Sciences*, vol. 1182, pp. 14–27, 2009.

[38] S. A. Rosenberg, J. C. Yang, D. E. White, and S. M. Steinberg, "Durability of complete responses in patients with metastatic cancer treated with high-dose interleukin-2: Identification of the antigens mediating response," *Annals of Surgery*, vol. 228, no. 3, pp. 307–319, 1998.

[39] E. Ishikawa, S. Takano, T. Ohno, and K. Tsuboi, "Adaptive cell transfer therapy for malignant gliomas," *Advances in Experimental Medicine and Biology*, vol. 746, pp. 109–120, 2012.

[40] T. M. Law, R. J. Motzer, M. Mazumdar et al., "Phase III randomized trial of interleukin-2 with or without lymphokine-activated killer cells in the treatment of patients with advanced renal cell carcinoma," *Cancer*, vol. 76, no. 5, pp. 824–832, 1995.

[41] D. F. McDermott, M. M. Regan, J. I. Clark et al., "Randomized phase III trial of high-dose interleukin-2 versus subcutaneous interleukin-2 and interferon in patients with metastatic renal cell carcinoma," *Journal of Clinical Oncology*, vol. 23, no. 1, pp. 133–141, 2005.

[42] M. B. Atkins, J. Sparano, R. I. Fisher et al., "Randomized phase II trial of high-dose interleukin-2 either alone or in combination with interferon alfa-2b in advanced renal cell carcinoma," *Journal of Clinical Oncology*, vol. 11, no. 4, pp. 661–670, 1993.

[43] S. Negrier, B. Escudier, C. Lasset et al., "Recombinant human interleukin-2, recombinant human interferon alfa-2a, or both in metastatic renal-cell carcinoma," *The New England Journal of Medicine*, vol. 338, no. 18, pp. 1272–1278, 1998.

[44] M. B. Atkins, J. Hsu, S. Lee et al., "Phase III trial of concurrent biochemotherapy with cisplatin, vinblastine, dacarbazine, interleukin-2, and interferon alfa-2b with cisplatin, vinblastine, and dacarbazine alone in patients with metastatic malignant melanoma (E3695): a trial coordinated by the Eastern Cooperative Oncology Group," *Journal of Clinical Oncology*, vol. 26, no. 35, pp. 5748–5754, 2008.

[45] D. F. McDermott, J. W. Mier, D. P. Lawrence et al., "A phase II pilot trial of concurrent biochemotherapy with cisplatin, vinblastine, dacarbazine, interleukin-2, and interferon alfa-2b in patients with metastatic melanoma," *Clinical Cancer Research*, vol. 6, no. 6, pp. 2201–2208, 2000.
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[46] O. Eton, S. S. Legha, A. Y. Bedikian et al., “Sequential biochemotherapy versus chemotherapy for metastatic melanoma: Results from a phase III randomized trial,” Journal of Clinical Oncology, vol. 20, no. 8, pp. 2045–2052, 2002.

[47] S. A. Rosenberg, J. C. Yang, D. J. Schwartzzuber et al., “Prospective randomized trial of the treatment of patients with metastatic melanoma using chemotherapy with cisplatin, dacarbazine, and tamoxifen alone or in combination with interleukin-2 and interferon alfa-2b,” Journal of Clinical Oncology, vol. 17, no. 3, pp. 986–975, 1999.

[48] C. Hamn, S. Verma, T. Petrella, K. Bak, and M. Charette, “Biochemotherapy for the treatment of metastatic malignant melanoma: A systematic review,” Cancer Treatment Reviews, vol. 34, no. 2, pp. 145–156, 2008.

[49] N. J. Ives, R. L. Stowe, P. Lorigan, and K. Wheatley, “Chemotherapy versus chemotheraphy for metastatic melanoma: A meta-analysis of 18 trials involving 2,621 patients,” Journal of Clinical Oncology, vol. 25, no. 34, pp. 5426–5434, 2007.

[50] S. J. O’Day, P. D. Boasberg, L. Piro et al., “Maintenance biotherapy for metastatic melanoma with interleukin-2 and granulocyte macrophage-colony stimulating factor improves survival for patients responding to induction concurrent biochemotherapy,” Clinical Cancer Research, vol. 8, no. 9, pp. 2775–2781, 2002.

[51] S. Kim-Schulze, B. Taback, and H. L. Kaufman, “Cytokine therapy for cancer,” Surgical Oncology Clinics of North America, vol. 16, no. 4, pp. 793–818, 2007.

[52] A. S. Guleria, J. C. Yang, S. L. Topalian et al., “Renal dysfunction associated with the administration of high-dose interleukin-2 in 199 consecutive patients with metastatic melanoma or renal carcinoma,” Journal of Clinical Oncology, vol. 12, no. 12, pp. 2714–2722, 1994.

[53] S. A. Rosenberg, M. T. Lotze, J. C. Yang et al., “Experience with the use of high-dose interleukin-2 in the treatment of 652 cancer patients,” Annals of Surgery, vol. 210, no. 4, pp. 474–485, 1989.

[54] S. A. Long, M. Rieck, S. Sanda et al., “Rapamycin/IL-2 combination therapy in patients with type I diabetes augments Tregs yet transiently impairs β-cell function,” Diabetes, vol. 61, no. 9, pp. 2340–2348, 2012.

[55] K.-I. Matsuoka, J. Koreth, H. T. Kim et al., “Low-dose interleukin-2 therapy restores regulatory T cell homeostasis in patients with chronic graft-versus-host disease,” Science Translational Medicine, vol. 5, no. 179, Article ID 179ra43, 2013.

[56] J. A. Bluestone, “The Yin and Yang of interleukin-2-mediated immunotherapy,” The New England Journal of Medicine, vol. 365, no. 22, pp. 2129–2131, 2011.

[57] E. Bonifacio, “Immunotherapy in type 1 diabetes: A shorter but more winding road?” Diabetes, vol. 61, no. 9, pp. 2214–2215, 2012.

[58] J. C. Steel, T. A. Waldmann, and J. C. Morris, “Interleukin-15 biology and its therapeutic implications in cancer,” Trends in Pharmacological Sciences, vol. 33, no. 1, pp. 35–41, 2012.

[59] NKTR-255: Nektar, http://www.nektar.com/pipeline/rd-pipeline/nktr-255.

[60] W. Xu, M. Jones, B. Liu et al., “Efficacy and mechanism-of-action of a novel superagonist interleukin-15: Interleukin-15 receptor αSu/Fc fusion complex in syngeneic murine models of multiple myeloma,” Cancer Research, vol. 73, no. 10, pp. 3075–3086, 2013.

[61] P. R. Rhode, J. O. Egan, W. Xu et al., “Comparison of the superagonist complex, ALT-803, to IL15 as cancer immunotherapeutics in animal models,” Cancer Immunology Research, vol. 4, no. 1, pp. 49–60, 2016.