

Autologous Natural Killer Cell/Natural Killer T Cell Immunotherapy of Malignant Diseases

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Received 7 July 2014; revised 6 August 2014; accepted 5 September 2014

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Abstract

Adoptive immunotherapy, the therapeutic infusion of *ex vivo* activated cancer-fighting white blood cells that was pioneered by Dr. Steven Rosenberg over 30 years ago, has become more widespread due to outstanding published research documenting the clinical efficacy of this strategy. Based on the well-established *in vivo* functions of NK and NKT cells, their integral role in the efficacy of certain chemotherapeutic and immunomodulatory agents, and their direct therapeutic action as displayed in clinical trials, the use of autologous natural killer cell infusions is an appropriate and warranted therapeutic option for the treatment of malignant diseases, especially in patients whose disease is refractory to standard treatments such as chemotherapy and radiation.

Keywords

Cancer, Immunotherapy, Autologous, Natural Killer Cells (NK Cells), Natural Killer T Cell (NKT Cells), Lymphocyte Activated Killer Cells (LAK cells)

1. Introduction

Cancer has recently surpassed heart disease as the leading cause of death in the United States. The American Cancer Society estimated 1,665,540 new cases of cancer in the U.S. in 2014, with 585,720 cancer-related deaths. While the most common treatments for cancer continue to be surgery, chemotherapy and radiation, recent developments in the field of immunotherapy have dramatically elevated the stature of this treatment option. Over the last 40 years, a state of broad-spectrum immune suppression has been repeatedly described in patients with virtually all pathologies of cancer. Decreased immune function and competency have been implicated as being independent prognostic factors of disease progression and poor survival rate in many types of cancer. The importance of natural killer cells (NK) in immune surveillance and early tumor rejection has been established by numerous published research studies and clinical trials. More recently, the role of natural killer T cells (NKT) in

How to cite this paper: Smith, A.J., Oertle, J. and Prato, D. (2014) Autologous Natural Killer Cell/Natural Killer T Cell Immunotherapy of Malignant Diseases. *Open Journal of Medical Microbiology*, 4, 192-202.

<http://dx.doi.org/10.4236/ojmm.2014.43021>

the regulation of immune responses has also been elucidated. Decreased number or function of NK and NKT cells tends to predispose patients to more aggressive tumor growth, with NK/NKT cell number and antitumor function continuing to decline as disease progresses [1]. NK cell and/or NKT cell activity and tumor infiltration rates have been established as independent prognostic factors in several malignancies [2]-[10]. Restoration of NK cell number and function by means of chemotherapy, immunomodulatory agents or adoptive immunotherapy typically leads to enhanced cellular immune response to tumor and higher survival rate, as demonstrated in animal studies and human clinical trials [2] [11]-[30]. Despite the seemingly universal *in vivo* immune suppression observed in malignancies, the *ex vivo* expansion and activation of antitumor effector cells, including NK and NKT cells, from cancer patients has been demonstrated. The use of NK and NKT cells as an effective component of adoptive immunotherapy protocols has been validated by clinical trials performed at Stanford University Medical Center and the University of Minnesota Cancer Center. However, these studies focused only on patients with Hodgkin's disease, non-Hodgkin's lymphoma or acute myeloid leukemia. The potential implications of immunotherapy involving autologous NK/NKT cells include longer life span of cancer patients in addition to cancer regression.

2. Natural Killer Cells and Natural Killer T Cells

In 1976, Herberman and colleagues were among the first to report that the cytotoxic activities of certain lymphoid cells were distinct from T-cell mediated cytotoxicity [31]. These cells were eventually termed "natural killer cells" due to their ability to spontaneously lyse tumor cells *in vitro*. Natural killer (NK) cells comprise roughly 10% of circulating peripheral blood lymphocytes in the body [32]-[35]. Despite their relative scarcity, NK cells are among the most important components of the immune system, especially the innate immune response. Classic NK cells are phenotypically CD3⁻CD56⁺, and are a distinct cellular subset from T lymphocytes, which are CD3⁺ [32] [33] [35]-[38]. The predominant characteristic of NK cells is their ability to kill cellular targets, including tumor cells and virally infected cells, without MHC restriction [32] [33] [35] [39]. In contrast, T cell-mediated cytotoxicity is restricted by MHC recognition. Because metastasized cancer cells generally lack MHC expression, NK cells are the body's primary defense against metastatic disease [32] [37]. NK cells are also potent producers of interferon-gamma, a key cytokine that drives antitumor cellular immune responses [34]-[36]. Perhaps most importantly, NK cells exert their cytotoxic effects with great specificity and without harming host tissue [34]-[36] [39].

Natural killer T cells (NKTs) have only recently been fully characterized phenotypically, and their importance in immune function and regulation is still being elucidated. While NK cells do not express CD3 or other classical T cell markers such as CD4 or CD8, NKT cells express surface markers common to both the T cell and NK cell [35]. NKTs are powerful regulators of the immune system, primarily through cytokine secretion [40] [41]. CD8⁺ NKTs exhibit potent anti-tumor activity *in vitro* and *in vivo*, and help coordinate the innate and adaptive immune responses, in part by their own prolific secretion of interferon-gamma [42]-[44].

3. Depressed NK/NKT Cell Function in Cancer

Over the last 30 years, a state of broad-spectrum immune suppression has been repeatedly described in patients with virtually all pathologies of cancer. In particular, the depressed ability of NK cells from cancer patients to lyse NK-sensitive cancer cells *in vitro* has been reported extensively [1] [11]-[16] [45]-[74]. In 1983, Balch and colleagues published a major study that assessed NK activity in 247 cancer patients and 146 age- and sex-matched controls [1]. In this cohort, patients presenting with either breast, colon, head and neck, or lung cancers had significantly depressed NK activity compared to controls [1]. In 1984, Strayer and colleagues noted a significant depression of NK activity in individuals with high familial incidences of cancer, compared to those with little or no familial incidences of cancer [45]. This trend was independent of sex, age and smoking habits [45]. Strayer's group later noted a specific correlation between low NK activity and familial incidence of breast cancer [46]. Significantly depressed NK activity has been reported in breast [46] [47], colon [48] and head and neck cancers [11]-[14] [49] [50], liver cancer [15] [51]-[53], leukemia [54]-[56], lung cancer [57] [63], melanoma [49] [57] [63], ovarian cancer [16] [65] [67], pancreatic cancer [68] [69], prostate cancer [70]-[73] and renal cell carcinoma [74]. Likewise, significant depression of NKT cell number and/or function has been noted in patients with breast cancer [75] [76], colon cancer [76], head and neck cancer [76], lung cancer [77] [78], melanoma [75]

[76], multiple myeloma [79], prostate cancer [80] and renal cell carcinoma [76].

4. Prognostic Significance of NKs and NKTs in Cancer Patients

Significant correlations between immune suppression and disease stage, disease progression, and survival rate have been described for several cancers [2] [11]–[30]. For example, loss of MHC Class I molecules from tumors, which results in NK cell activation, is prognostic of increased survival in breast cancer [17]. Natural killer cell number and/or function have been identified as independent prognostic factors in many cancers, including breast [18], colon [19]–[21], gastric [23] [24] and head and neck cancers [11] [14] [25] [26], liver cancer [15], leukemia [27], non-Hodgkin's lymphoma [28] and ovarian [16] [29] and prostate [30] cancers. Depressed NK function or number is prognostic of increased risk of recurrence, metastasis, and death, whereas increased NK function is prognostic of decreased incidence of metastasis and increased chance of progression-free survival and overall survival [2] [11]–[30]. Further, the intensity of NK cell infiltration into tumors, evaluated by histochemical analysis, is also of prognostic value in colon cancer [2]–[4], gastric cancer [5] [6], lung cancer [7] [8] and renal cell carcinoma [9]. Additionally, NKT cell infiltration is a prognostic factor in colon cancer [10]. As is the case with NK activity and tumor infiltration, increased NK/NKT infiltration is prognostic for decreased incidence of metastasis, increased chance of progression-free survival and overall survival.

Several studies have demonstrated the ability of chemotherapeutic agents, such as paclitaxel [81]–[83], docetaxel [83] [84], tamoxifen [85] [86], cimetidine [16] and indomethacin [87], to enhance NK activity in cancer patients. Researchers at Harvard University have demonstrated that multiple myeloma patients responding to thalidomide treatment exhibited significant increases in NK cell number and anti-tumor activity than did non-responding patients [88] [89]. In these studies, thalidomide directly enhanced NK function against multiple myeloma cells [88] [89]. Similarly, patients with gastrointestinal stromal tumors that received and responded to Gleevec, exhibited a significant increase in NK function compared to non-responding patients [90].

5. Expansion of Anti-Tumor Effector Cells from Cancer Patients

Despite the seemingly universal *in vivo* immune suppression seen in malignancy, several published studies have demonstrated the feasibility of expanding potent anti-tumor effector cells from the blood of patients with virtually all types of malignancy [91]–[104] [105]–[122]. The *ex vivo* expansion of NK, NKT, and lymphocyte-activated killer cells (LAK) cells for non-immunotherapeutic purposes has been described for patients with hepatocellular carcinoma, leukemia, lung cancer, ovarian cancer, and prostate cancer. Peng and colleagues demonstrated that activated NKs can be efficiently expanded from hepatocellular carcinoma (HCC) patients [91]. NKs and/or NKTs have been successfully expanded and activated from the peripheral blood of patients with acute myelogenous leukemia [92] [93], chronic myelogenous leukemia [94] [95], acute lymphocytic leukemia [96] and chronic lymphocytic leukemia [97] and in each instance these expanded cells exhibited *in vitro* cytotoxicity against either autologous or allogeneic leukemia cells. LeFever *et al.* noted that LAK cells could be expanded from lung cancer patients despite significant baseline depression of *in vitro* cytotoxicity against tumor targets [61]. Allavena and Lucci reported similar results in generating functional LAK cells from ovarian cancer patients [65] [98]. Activated NKs and NKTs have been expanded from the blood of prostate cancer patients, with these cells showing potent cytotoxicity against prostate cancer cell lines *in vitro* [99] [100].

6. Adoptive Immunotherapy of Cancer

Dr. Steven Rosenberg of the National Cancer Institute first reported in 1985 that the administration of LAKs could achieve clinical responses in patients with colorectal cancer, lung cancer, melanoma or renal cell carcinoma [101]. Rosenberg's later studies demonstrated the safety, efficacy and minimal toxicity of LAK cell infusions in these patients [102]–[104]. LAK cells are generated *in vitro* using high-dose cytokines, namely IL-2. The antitumor effect of LAK cells has been shown to be mainly due to the presence of NK cells in the LAK population [32] [37] [38] [123]. Rosenberg's group eventually focused solely on the adoptive immunotherapy of malignant melanoma [105]–[108]. Most recently, this group reported that 18 of 35 metastatic melanoma patients treated with adoptive immunotherapy experienced objective clinical responses, defined as a minimum 50% reduction in tumor burden [107] [108].

In vitro generation of autologous effector cells for adoptive immunotherapy of cancer has been repeatedly

shown to be feasible. Adoptive immunotherapy has been demonstrated to be safe, well-tolerated and to have at least modest efficacy in the treatment of human cancers, including breast cancer [109], gliomas [110]-[113], liver [114] and lung [115] cancers, lymphoma [116], leukemia [117], ovarian [118] [119] and pancreatic [120] cancers, and renal cell carcinoma [121] [122]. Specifically, NK or NKT cell-based immunotherapy has been utilized in breast cancer [109], gliomas [111], hepatocellular carcinoma [114], Hodgkin's and non-Hodgkin's lymphoma [116], acute myelogenous leukemia [117], renal cell carcinoma [122], colorectal carcinoma [124], gastric carcinoma [125], nonsmall cell lung cancer [126], with clinical success. Miller *et al.* reported complete remissions in 5 of 19 poor prognosis AML patients treated with NK cell infusions and high-dose cyclophosphamide and fludarabine [117]. Following immunotherapy consisting of autologous NKT cell infusions, Leemhuis and colleagues reported clinical responses in 4 of 9 Hodgkin's/non-Hodgkin's lymphoma patients who were previously refractory to chemotherapy [116]. Further, the ability of NK cells to infiltrate and eliminate metastatic tumors has been demonstrated in humans and in animal models [4] [7] [121] [127]-[129].

Recently, a method for the clinical-scale expansion and activation of natural killer cells and natural killer T cells for adoptive immunotherapy purposes has been reported. [130] Recent clinical trials involved NKT cell-targeted immunotherapy for patients with non-small cell lung cancer was well tolerated with no severe adverse events associated with the cell therapy [131] [132]. A significant increase in peripheral blood mononuclear cells (PBMC) production of IFN- γ was detected in 10 of the 17 patients that received treatment [133]. Alpha-galactosylceramide (α -GalCer)-reactive IFN- γ forming cells look as if they included both NKT and NK cells [134] [135]. Even though these patients did not show significant tumor regression, a significantly prolonged median survival time (MST) of 29.3 months for patients with higher IFN- γ as compared to a MST of 9.7 month those with lower IFN- γ levels [133].

7. Concluding Remarks

The adoption of immunotherapy as a means to treat cancer has recently been reinvigorated in scientific discussion. Autologous NK/NKT treatment has potential to increase the life span as well contribute to cancer regression. The decrease in immune response after chemotherapy makes patients vulnerable to infectious causes of cancer in addition to reducing the capacity for the immune system to stave off cancer respectively. Autologous NK/NKT cultured in *ex vivo* should be well received among patients with attenuated immunity. Although the capacity of immune surveillance of cancer differs among individuals and individual cancers, the opportunity to treat patients with immunotherapy should be considered as an option to be sure that those circumstances are indeed the case. The current state of autologous immunotherapy with cells cultured in *ex vivo* is currently expensive. Further development, research and advances in the field of immunotherapy may reduce the cost making autologous NK/NKT treatment more available to patients in the near future. With the promising findings, more research should be performed to perfect and direct the autologous NK/NKT treatment for improvement in patient outcomes.

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