Brief Report

Immunotherapy in Metastatic Malignant Melanoma and Non-Small Cell Lung Cancer; a Brief Review and Position Statement from the Immuno-Oncology Clinical Forum (IOCF), Iran

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Abstract

Given the unmet needs in cancer treatment, extensive research and development has evolved to offer therapies for cancers to extend survival and minimize side effects. Immunotherapy, an approach to harness normal immune cells against cancers not only today's breakthrough but in fact the future of oncology therapeutics. Taking into consideration the recent approvals for new lines of therapy including anti-programmed-death-1 or programmed-death-1 ligand (PD-1/PD-L1) monoclonal antibodies for the treatment of Malignant Melanoma (MM) and Non-Small Cell Lung Cancer (NSCLC), local strategies need to be established following the field experts' concurrence. Expert input forums are among the key approaches to define locally-adapted clinical-pathways with regard to the novel treatments. To this end, a panel of Iranian medical oncology experts reviewed the available evidence, taking into consideration recent practice guidelines with regard to the treatment of MM and NSCLC in order to draw an agreed-upon approach highlighting the position of immunotherapy in their current practice. Having addressed the key questions and considering the possible limitations and challenges, the panel could reach an agreed position. This report highlights the discussions with regards to the role of immunotherapy in MM and NSCLC during the immune-oncology clinical forum (IOCF) comprising an Iranian panel of experts.

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Introduction

Efficient cancer treatment is regarded as an urgent yet unmet medical need. Most current cancer treatments such as chemotherapy target the cancer cells non-specifically, causing the immune system to attack healthy and normal cells and lead to serious and even life-threatening toxicities (1, 2). Accordingly, there is a shift from the traditional treatment modalities to less-toxic and more advanced targeted options such as immunotherapy (3). Immunotherapy appears to position itself not only as "today's" breakthrough but also the "tomorrow" of oncology therapeutics. The goal of immunotherapy is to help achieve durable eradication of cancer and induce long-term remission through harnessing the patients' own immune system to fight cancer with as minimal toxicity as possible (4). Immunotherapy focuses on exploiting the immune checkpoints inhibition, which is a mechanism used by tumor cells to evade the immune system(4). Emerging research has characterized the programmed cell death protein-1(PD- 1) as one of the immune checkpoints exploited by tumor cells.PD-1 and its ligands PDL, PD-L1 and PD-L2, form an important immune checkpoint pathway to reduce the peripheral T-cell immune response against self-antigens. PD-1 in known as an important mechanism shared by many tumors to evade the T-cell immune response (3, 5-9).

Given the promising clinical benefits of immunotherapy in certain tumor types, clinicians need to know about global recommendations, and preferably, locally-adapted guidelines when deciding to use such therapies in their practice. Normally, incorporating the new lines of treatments into current protocols, requires field experts' concurrence. To reach this, holding experts forums would help analyzing the current status, evaluating the available evidence, assessing risks versus benefits, and arriving at shared decisions on treatment algorithms with regard to novel options.

This report is an overview of discussions within the Immuno-Oncology Clinical Forum (IOCF), Iranian panel of medical oncology experts, held in September 2015. The present article provides a brief literature review on clinical issues in the management of advanced malignant melanoma (MM) and non-small cell lung cancer (NSCLC) in immune-oncology era, as well as the panel's position on applying novel treatment strategies including immunotherapy in such cancers.

The aim of this report is to highlight the current management strategies and new treatment approaches in MM and NSCLC based on the available evidence and IOCF experts' inputs. The present document is expected to be of interest and clinical reference for specialists in oncology who are involved in the management of the above malignancies. Continued discussions in future forums would potentially pave the way towards establishment of locally-adapted guidelines on immunotherapy in cancers.

The expert panel composition, key questions and discussion approach

A panel of experts from medical oncology field discussed the current evidence, limitations and clinical peculiarities in the management of MM and NSCLC in Iran and deliberated the opportunities for optimal use of immunotherapy in these cancers. Each participant was enrolled based on his/her clinical expertise and academic records in the field of oncology. All experts interacted in key question-based round-table discussions during this forum. Through a systematic approach toward key issues in MM and NSCLC management including: 1-the response criteria following treatment, 2- potential therapeutic options and their limitations, 3- key benefits of the novel immunotherapies on treatment response goals and 4- the significance of biomarkers and their assessment; the available evidence together with experts' inputs/responses were compiled to reach an agreed-upon position.

Moderators of the IOCF proposed several questions related to the novel treatment approaches in MM and NSCLC. These key questions (KQs) were defined 15 days prior to the forum with selected KQs isolated and ranked by priority. As such, 5KQs were selected to be explicitly discussed answering to which could provide a practical insight into the novel treatment strategies (namely, immunotherapy) in MM and NSCLC.

The panel attempted to systematically review the evidence in response to each KQ and evaluated the outcomes of interest for each question based on the treatment response criteria including the overall survival (OS) and quality of life (QOL). The addressed KQs during the IOCF are outlined below.

KQ1: When treating cancer in advanced stages, the goal of treatment is progression-fee survival (PFS), OS, QOL, etc. What protocols (based on certain pre-defined patient criteria) are practically followed in our practice?

KQ2: What are our potential options in treating stage-IV melanoma? How do we decide on which option to take and what are the challenges faced with each potential option (i.e. first-line, second-line or combination therapies)?

KQ3: Given the advent of new immunotherapies (ipilimumab, nivolumumab, pembrolizumab), how shall we consider their key benefits in treatment response goals in MM and NSCLC?

KQ4: How shall we see the significance of biomarkers? Are we testing for any regularly? Which biomarkers testing techniques are currently available in our setting?

KQ5: What options do we practically consider in treating stage IIB and IV NSCLC? How do we decide on which option to take and what are the challenges faced with each potential option (i.e. first-line, second-line or combination therapy)?

Results and Discussion

- *Malignant melanoma; highlighting the current practice*

Based on the available reports from comprehensive registries over the past 15 years in our country, the annual incidence of cutaneous MM ranges from 0.2 to 0.4 per 100,000, which has remained relatively constant over the past decade (10).

In a report from the Dermatology Center of Excellence in Iran, 6.5% of the tumors diagnosed during 2008-2012 were malignant melanomas (11). The 5-Year survival of MM in our setting is 28.6% which is far less than the developed countries .According to local data; many patients present in their advanced/metastatic stage upon diagnosis (Clark 3 and beyond) and the most prevalent site is head and neck (10,11).

With regard to treatment, despite huge global experience with the use of traditional chemotherapy for metastatic melanoma, almost no evidence supports true survival benefits (12-15). New options including biologic therapies (BRAF inhibition as well as PD-1 or cytotoxic T-lymphocyte-associated protein 4,-CTLA-4- receptor inhibitors) have been characterized as preferred options rather that classic chemotherapy agents by the most recent guidelines laid down by the National Comprehensive Cancer Network (NCCN) (16, 17).

Dacarbazine, temozolomide, conventional and pegylated interferon alpha, and imatinib appear to be the current first-line for MM practice in Iran (11). In the event of refractoriness, taxanes and platinum-based regimens are the preferred second-line. This is somehow compatible with the recommended option from the latest guidelines (17).

So far, there seems to be quite a minimal experience with ipilimumab (IPI) for previously-untreated advanced (unresectable or metastatic) melanomas amongst Iranian medical oncologists. Since pembrolizumab (PZB) and nivolumab (NVB)are currently approved for advanced melanoma in patients with disease progression following IPI and, if BRAF V600(a human gene that makes the protein B-Raf) mutation positive, a BRAF inhibitor; perhaps a fraction of cases can also be considered for these novel options(18, 19).

Considering the available evidence and current practice trends (20-35), the novel treatment option are shown to provide favorable efficacy and safety profiles. The cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) blocking agents such as ipilimumab and selective BRAF inhibitors (if BRAF V600; mutation is positive), including vemurafenib are the preferred first-line options. Meanwhile anti PD-1 antibodies including pembrolizumab and nivolumab have demonstrated dependable efficacy and proper safety as second-line. The so far local experience with ipilimumab and vemurafenib has remained relatively scant. Taking cost versus utility issue into account, alternative treatment with PD-1 inhibitors may effectively serve treatment response goals in advanced metastatic malignant melanoma.

- *Non-small cell lung cancer; highlighting the current practice*

Lung cancer is considered the fifth leading cancer in Iran. The prevalence rate of this cancer has been increasing over the last decade(36).Non-small cell lung cancer (NSCLC) accounts for 28.5% of all-type lung cancers in Iran, while adenocarcinoma, squamous cell lung cancer, SCLC and other lung cancer types comprise 28.9%, 19%, 18.6% and 5% of the cases (37).Patients tend to predominantly present in advanced-stage tumor in lung i.e. stage III b or IV (almost 75% of instances). Thus, relapse and systemic metastases are common in our practice (37).

Studies indicate an estimated number of 2200 cases and 2030 deaths of lung cancer in Iran per year. The annual prevalence of all-type lung cancers in Iran is estimated at 0.0026% with a nearly one third share for NSCLC. The annual incidence of NSCLC in Iran is estimated to be 0.00072% (37).

Despite the level-best care through the current therapeutic approaches in NSCLC, the mean OS remains around 18 months (38).

With regard to the local treatment approaches, surgery is the first step in most cases. Adjuvant chemotherapy with or without mediastinal radiotherapy becomes the next step agreed by almost all experts. Medical oncologists are those who are mainly involved in chemotherapy of NSCLC cases. Our current trend includes using cisplatin-based regimens as fist-line. Following relapse,

second-line chemotherapy would include taxanes, namely docetaxel (39). According to the local literature and evolving trends (3,40-48), integrating targeted therapies and immunotherapy in lung cancer care appears to be warranted.

Having addressed KQs 1-5 and taking the existent evidence and current practice trends into account (40-48), the panel reemphasized that mutations in EGFR (epidermal growth factor receptor) or ALK (anaplastic lymphoma kinase)drive the targeted-therapy selection, while patients with negative status for these biomarkers have their therapy guided by histology and further clinical factors. Availability and affordability of targeted- or immune-therapies may hinder the selection of the preferred choice in some instances.

- *The immuno-oncology perspective*

The role of immune checkpoints in modifying the functional profile as well as characteristics of T cell responses is progressively articulated in molecular detail(49-54). In-depth understanding of the biology of melanoma and its interface with the immune system have contributed to the advent of blocking antibodies to the PD-1 pathway and one of its ligands, PD-L1(6, 24, 55-59).With the significant clinical benefits and appropriate safety and tolerability profile, the blockade of inhibitory receptors have been shown to reestablish T cell function in cancer. This has been effectively translated to novel options in the treatment of cancers including malignant melanoma (24).

While the blockade of immune-regulatory checkpoints subsides T-cell responses to melanoma upon PD-1/PD-L1 modulation and demonstrates a clinically-tested response for cancer immunotherapy, combinations of these agents with other already-established anti-melanoma agents would possibly result in even further benefits (60).

The monoclonal antibodies (MAbs) which block CTLA-4 and PD-1 have recently been approved for the treatment of metastatic melanoma(61). Indeed, the anti-PD-L1 blocking antibodies have provided robust clinical benefits in patients with several solid tumor including bladder, lung and head and neck carcinomas (62,63). Such a remarkable therapeutic potential of PD-1/PD-L1 immune checkpoint blockade necessitates the need to identify applicable biomarkers to warrant their optimal clinical application (64).

Quantitative imaging techniques and T cell receptor (TCRs) sequencing in metastatic melanoma before and during anti-PD-1 therapy (pembrolizumab) have corroborated that responding patients have increased numbers of proliferating CD8+ T cells (52). It has also been shown that pre-treatment samples from responding patients (at the invasive tumor margin and within the tumor itself)retain higher numbers of CD8+ T cells with a clonal TCR in close connection with PD-1 and PD-L1 expressing cells (52). This suggests the possible link between pre-existing density of CD8+ T cells at the invasive tumor margins as a biomarker of response(65). Owing to the potential clinical implications of such findings, prospective validation in randomized, controlled-clinical trial has gained attention. As such, towards the immune classification of malignancies as part of the diagnostic and prognostic evaluation of tumors, an initiative entitled Immunoscore Project has been launched(66). An emerging body of evidence on response to PD-L1 immuno-modulatory antibodies has postulated that the common mechanistic activity depends upon adaptive PD-1/PD-L1 status and the pre-existing CD8-mediated immune response within this immune inhibitory axis(67-69).

From the immunological viewpoint, it has been speculated that reactivated CD8+ T cells are of the memory lineage rather than purely effector T cells. This insight has recently explained CD8+ T cell exhaustion phenomenon in various tumor types (70).

The PD-1/PDL-1 pathway blockade has offered clinically-significant efficacy in patients with advanced NSCLC, melanoma, renal-cell cancer, and Hodgkin's lymphoma which have been refractory to conventional lines of therapy (71, 72). The extant evidence suggest that this blockade is specifically effective in subjects with pre-existing cellular immune response (73). On the other hand, the activation and invasion of T cells, regulated by type-1 interferon response, appears to predict the therapeutic benefits from PD-L1–PD-1 blockade alone. Moreover, PD-L1 expression, particularly by the tumor-infiltrating lymphocytes (TILs), warrants its prospective validation as a potential biomarker in clinical trials assessing the efficacy of PD-1/PD-L1 antibody-containing regimens. Nevertheless, the implication of Clinical Laboratory Improvement Amendments (CLIA)-based validated assays for PD-L1 expression and the potential complexities of the tumor-host response need to be considered as they may affect the outcome of any given single or combined intervention (74).

Owing to the impressive clinical activity of PD-1 or PD-L1 inhibitors in specific patients of different cancers, the foundational impact of immune-related interventions in cancer has been well-recognized and treatment indications are being defined. It should however be noted that distinct subset of cancers are much less infiltrated with immune cells (75) and when type-I interferon-regulated genes,

T cell–related genes, and PD-L1 are less expressed, prognosis is generally poor (76). Thus, immune therapies which harness CD8+ T cell infiltration would potentially be more effective in patients who show no or minimal response to these treatments. Chemotherapy and targeted therapies as well as radiotherapy are being exploited here as they are likewise found to trigger immunogenic cell death, intra-tumoral T-cell infiltration, and enhance antigen presentation. Furthermore, the possible added value of combination therapies using immune-checkpoint inhibitors with cytokines such as IL-2, IL-15 or type-Iinterferon and chemotherapeutic agents need to be examined in patients failing to respond or relapse on such treatments. In addition, since tumors hijack vascularization, a potential way to potentiate clinical benefits may be the combination of immunotherapy with biologic agents to regularize tumoral vasculature letting further immune cells influx into the tumor (52).

The recent immunotherapy success seems to presage abeckoning future by virtue of continued research endeavors in the field of immune-oncology.

Pembrolizumab and nivolumab are among the foremost anti-PD-1 antibodies which are being/have been tested in different cancers including but not restricted to melanoma, non-small cell lung cancer, renal cell carcinoma as well as head and neck cancers and lymphoma(24, 77, 78). This review was as attempt to discuss the evidence supporting the efficacy of anti-PD-1 antibodies in cancers, namely MM and NSCLC, as well as their combination with other anti-cancer agents in future directions of clinical trials to help increasing the number of long-term survivors. In addition, this report highlighted the position of a group of medical oncology experts and their position to incorporate these novel therapies in their practice.

Concluding remarks and future directions

Based on the present position statement from the IOCF2015, immunotherapy is expected to progressively find its way in our treatment approach in MM and NSCLC, depending on the availability and cost versus utility issues. Such novel approaches would be expected to be soon positioned in international guidelines on MM and NSCLC treatment which were reviewed in this paper. The present report would hopefully provide the basis for the development and implementation of locally-adapted guidelines on cancer immunotherapy approaches in the future.

Competing Interest

The present report outlined the communications and experts' opinions during the Iranian IOCF held on 28 September 2015. The authors declare no competing interest upon data review, talk delivery during the meeting, interactive discussions and preparation of the present report. MTN and AG provided medical consultancy to Behphar Scientific Committee, Behphar Group, Behestan Darou, Tehran, Iran.

Authors Contribution

Tfayli A. contributed to session moderatorship, literature review and plenary talk as well as summary of recommendations. Attarian H., Ghadyani M., Ghotb A., Mashadian M., Salimi B., Sedaghat S., Seghatoleslami M., Seifi S., and Torabi-Nami M. equally contributed to this position statement through inputs and critical reversion of themanuscript for important intellectual content (sorted alphabetically as second-order authors). Torabi-Nami M.drafted the manuscript. Torabi-Nami M. and Ghotb A. provided technical material support. All authors read and approved the final manuscript.

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