Oral Oncology xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Review

Immunotherapy in head and neck cancer: Harnessing profit on a system disruption

Chloé Rancoule [a], Alexis Vallard [a], Sophie Espenel [a], Jean-Baptiste Guy [a,b], Yaoxiong Xia [a], Anis El Meddeb Hamrouni [a], Claire Rodriguez-Lafrasse [b,c], Cyrus Chargari [d,e,f], Eric Deutsch [d], Nicolas Magné [a,b,*]

[a] Radiotherapy Department, Lucien Neuwirth Cancer Institute, St Priest en Jarez, France
[b] Radiobiology Laboratory, Lyon Medicine University, Lyon, France
[c] Hospices-Civils-de-Lyon, Lyon Hospital, Lyon, France
[d] Radiotherapy Department, Gustave Roussy Campus Cancer, Grand Paris, France
[e] INSERM 1030, Molecular Radiotherapy, Gustave Roussy Campus Cancer, Grand Paris, France
[f] Institute of "Recherche Biomédicale des Armées", Paris, France

ARTICLE INFO

Article history:
Received 18 May 2016
Received in revised form 26 July 2016
Accepted 4 September 2016
Available online xxxx

Keywords:
SCCHN
Immune system
Immunotherapy
Monoclonal antibodies
Clinical trials
Treatment combination

ABSTRACT

Immune system deregulation and evasion play a key role in cancers' evolution and progression, including squamous cell carcinoma of the head and neck (SCCHN). Development of basic research proposed a whole new vision of cancer treatment, based on a strong biological rational, and targeting intrinsic deregulations. Immunotherapies provide an encouraging strategy for patients' improved outcomes. Immune-based therapies could act on cancer growth and/or development throughout many pathways. If cetuximab is for now the only monoclonal antibody approved for SCCHN management, other strategies, e.g. immune checkpoints openers, are arousing enthusiasm. Clinical trials are multiplying in patients with recurrent/metastatic SCCHN and primary results offer promising outcomes. Prospects of combining various immunotherapies with more established treatments, such as chemotherapy and radiotherapy, seem very encouraging and could provide synergistic benefits. Ongoing phase III clinical trials should soon enlighten us on the next "standard of care" for SCCHN. In the present review we summarized the different immunotherapy strategies that are currently under clinical investigation for SCCHN' medical care.

Immunotherapy general concepts

The notion developing that the intrinsic immune system acts as a functional cancer immune-surveillance process and a cancer development's regulator is experiencing a huge interest.

First experiments with immune-deficient mice have provided data supporting the role of adaptive immunity in cancer immune-surveillance [1]. Tumor cells can express antigens and become the targets of a T cell–mediated adaptive immune response [2,3]. Tumor cells release cancer antigens. These antigens are captured by antigen-presenting cells which present them to the T cells. Then the T cells start to proliferate and to kill tumor cells [4]. Indeed, the differentiation of naïve $CD4^+$ T cells into T helper type 1 cells producing interferon gamma (IFN-γ) promotes CD8 T cell–mediated adaptive immunity [5]. Thus, tumors contain infiltrates of immune cells. Galon et al. described that tumor infiltrating lymphocytes (TIL) play a significant role in patients' clinical outcome [6,7]. TIL grade (depending on its density (0–3: slight, moderate or high) and on its distribution (focal, multi-focal or diffuse in the whole tumor)) is associated with progression-free survival. Patients with TIL grade 3 tumors had 100% survival at 5 years [7]. Thus TIL are good prognosis factors in melanoma, colorectal, breast and ovarian cancers.

If our cells are able to recognize and eradicate tumor cells, the cancer cells develop different mechanisms to evade immune destruction: sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, and activating invasion and metastatic processes. Cancer cells and tumorigenic micro-environment (stromal cells and surrounding normal tissue) act together for tumor development and progression [8,9]. The innate immune system and the cancer-related inflammation are involved in both tumor initiation and progression [10] and a better understanding of their action

* Corresponding author at: Head of Radiotherapy department, Director of Research and Innovation Center, Lucien Neuwirth Cancer Institute, 108 bis, Avenue Albert Raimond - BP 60008, 42270 Saint-Priest en Jarez cedex, France.
E-mail address: nicolas.magne@icloire.fr (N. Magné).

http://dx.doi.org/10.1016/j.oraloncology.2016.09.002
1368-8375/

mechanisms could be a key element of cancer clinical management.

Since the early 2010s, the interest concerning immunotherapy (IT) against cancer is intense. If up until today the IT is not frequently used in the medical current practice, the increased number clinical trials symbolizes the infatuation for this new approach. There are basically 2 methods to target the immune system. If the immune system does not recognize the tumor as foreign, we have to induce a response by teaching it to recognize the tumor as dangerous. If the answer exists, but is not strong enough, it will be necessary to stimulate it.

IT in the oncology landscape is nowadays represented at different levels.

- monoclonal antibodies that are able to target molecules expressed on the tumor or the immune cells' surface and induce thus a functional blockade of the tumor growth,
- adoptive cell transfer (of the patient him-self or genetically produced) that are specific for a tumor antigen [11],
- therapeutic vaccines which could be preventive (such as vaccines targeting papillomavirus for cervix and hepatitis B for liver) or curative (as the sipuleucel in prostate cancer),
- and immune system stimulators (e.g. interleukin 2 or interferon for melanoma and renal cell cancers).

Monoclonal anti-bodies (MAB) therapies are currently the most widely used form of IT in cancer patients [12]. MAB directed against CD20 and HER-2 are the standard of care in hematopoietic malignancies and breast cancer, respectively. A large number of monoclonal antibody drugs are already available and clinical trials are investigating new ones in order to treat several types of cancer.

They can act through various ways targeting several pathways in order to block or limit tumor progression:

- MAB can make the cancer cell more visible to the immune system. For example, rituximab attaches itself to a B cells specific marker: the CD20 protein. B cells are arising in certain types of lymphomas. Rituximab attachment on B cells makes the cells more visible to the immune system which can then attack the cancer cells [13]. MAB can also tag the cancer cells for destruction by killer immune cells by forming a bridge between a tumor cell and an immune cell. This antibody-dependant cell toxicity (ADCC) links the innate immune cells (natural killer and dendritic cells) and the cancer cell which lead to a cytotoxic response [14].
- MAB can block growth or proliferative signals. Cetuximab is approved to treat colon cancer and head and neck cancers. It attaches to epidermal growth factor receptors (EGFR) on cancer cells and consequently blocks EGF signal. This blockade slows or stops the cancer growth [15].
- MAB can stop neo-angiogenesis. Bevacizumab targets vascular endothelial growth factor (VEGF) delivered by cancer cells in order to attract new blood vessels and blocks its signalization [16].
- MAB can activate T cell proliferation. PF-04518600 is a MAB that recognizes the co-stimulatory receptor OX40 at the surface of T cells which induces their proliferation and activation.
- MAB can also act as a vector targeted against a tumor antigen which carry and address a specific treatment to the tumor. For example, ibritumomab targets radioactive particles [17]. Ado-trastuzumab emtansine fixes HER2 receptors, then it is ingested in the cancer cell cytoplasm where it finally releases its cytotoxic load [18].
- MAB can target immune check point openers. This last category is particularly promising today. Indeed the lift of immune system inhibition appears stronger than all the strategies that have been developed to activate it [19]. The release of the immune system should definitely usher immunotherapies [20]. There are now 8 immune checkpoints described and the best known are the CTLA4, and the couple PD1 PD-1 ligand. anti-PD1 and anti-PDL1 are particularly on a roll [21]. Expressed on T cells surface, PD-1 (programmed cell death) binds PD-L1 expressed on tumor cells surface. This interaction makes the tumor cell "invisible" to the immune system by turning off (or disarming) T cells and by this way it drives tumor evasion from immune attack. Initial phase I trials with anti PD-1 or anti-PD-L1 MAB have shown significant efficacy with response rates of 18–28% and 10–17% respectively in patients with advanced melanoma, non-small cell lung cancer, and renal cell carcinoma [22,23]. Moreover, less toxicity was described compared to the previous reported trials investigating CTLA-4 blockade [24]. anti-PD-1 drugs have been developed at a phenomenal speed, taking just three years from the first clinical trials to the first approval, evolving into FDA and EMA authorizations for nivolumab in melanoma patients (from FDA as 2nd-line in December 2014 and as 1st-line in September 2015 in combination with ipilimumab; from EMA in June 2015 as 1st and 2nd-line) and in NSCLC (from FDA in March 2015 and from EMA July 2015 for squamous NSCLC; from FDA in October 2015 for non-squamous NSCLC). Pembrolizumab get authorizations too for melanoma as 1st-line (from FDA in September 2014; and from EMA in July 2015) and for NSCLC as 2nd line (from FDA in September 2015). Multiple other clinical trials are ongoing in multiple other solid tumor types including patients with SCCHN.

If IT gains ground in the oncology research field, the observed disparity in treatment response rates between the patients and the early positive responses that end in failure strongly suggests a role for immune escape. Tumor escape from cancer immunotherapy differs from traditional drugs' resistance. For most anticancer therapies, such as chemotherapy or targeted therapy, resistance to treatment can be mediated by the expression of specific proteins such as drug efflux pumps, by the loss of expression of the therapeutic target, or the up-regulation of compensatory signaling pathways. Immunotherapies potentiate an anticancer intrinsic T-cell response. Different studies evidenced several strategies of cancer cells to evade immune recognition and destruction. Among them we can described in SCCHN: the disruption of the antigen-presenting machine [25–27], the development of cancer-permissive tumor microenvironment [28–30] and an anergy of immune effectors cells (in both peripheral T lymphocytes and TILs) [31–35]. The existence of these numerous escape mechanisms is still a barrier to IT success. Efforts to understand them are necessary to don't drop the enthusiasm in this new therapeutic landscape.

Immune system and SCCHN

Squamous cell carcinoma of the head and neck (SCCHN) is the fifth most common cancer worldwide, with a global annual incidence of 600 000 cases. SCCHN represents a heterogeneous group of tumors, which encompasses a variety of tumors originating in the lip/oral cavity, hypopharynx, oropharynx, nasopharynx, or larynx. Despite multimodal treatments' advances and innovations for recurrent or metastatic disease [36], the prognosis remains poor. The therapeutic challenge is thus important and some clinical evidences propose the immune system as an interesting target. SCCHN has been intensely studied these last few years, because of its poor prognosis and the relative ease of tissue acquisition

Please cite this article in press as: Rancoule C et al. Immunotherapy in head and neck cancer: Harnessing profit on a system disruption. Oral Oncol (2016), http://dx.doi.org/10.1016/j.oraloncology.2016.09.002