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Immunotherapy for Malignant Gliomas: A Roadmap for the Future

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1. Introduction

Since many decades, medical doctors and researchers have been intrigued by the possible beneficial contribution of the immune system in the long-lasting combat against cancer. Both in the cellular and humoral immunity arms, powerful tools are available to target the cancer cell. Moreover, the gradual shift of a focus on aspecific reinforcement of the innate immune system towards a specifically activated adaptive immunity in order to reject cancer cells has dominated the field of the last 10 to 20 years(1). Restorative immunotherapy in which cytokine balances are restored or reset and aspecific adoptive immunotherapy using e.g. natural killer (NK) cells or lymphokine-activated killer (LAK) cells are classical representations of the first wave. Specific adoptive immunotherapy using ex vivo activated antitumor cytotoxic T cells and especially active specific immunotherapy ('cancer vaccines') are representative for the second wave. Thorough changes in the underlying basic immunology mechanism guide these novel approaches. To date, only the different variants of cancer vaccines are able to induce an immunological memory, as such being the only approach potentially protecting the patients for future cancer re-challenges(2). A perceived low rate of classical objective responses, restricted to volume changes of a measurable tumor burden, has been the principal body of criticism against these therapies.

Several new insights however, especially focusing on changes in the micro-environment of the tumors, are only starting to be unraveled. Without any doubt, they're already now revealing much more than the previous tips of the curtains. Nowadays, converging evidence is being gained in a rapid way, for the need to move towards a third wave of immunotherapy approaches, those of the multimodal integrated immunotherapy paradigms, considering all the relevant players in the complex field of tumor immunology.

2. Proof of the principle: A solid body of preclinical evidence

The idea to actively prime cytotoxic T cells to specifically kill a tumor target cell has become a well established scientific fact. Several approaches all aiming to induce specifically activated, tumor-rejecting effector T cells have been investigated and found to be reproducible and reliable technologies. Genetically engineered tumor cells but especially autologous dendritic cells charged with tumor associated antigens have become the most

potent and popular immunological adjuvants to install an active anti-tumoral immunity(3;4). An additional advantage of the latter is the activation of both the innate and adaptive immunity arms of the patient. The mechanisms underlying this antitumoral priming capacity of dendritic cells seem to be fully consistent with the established paradigms of antigen uptake, processing and presentation. The exclusive potential of DC to present and cross-present exogenous antigens in the same antigen presenting cell is the critical characteristic for a successful antigen presentation to cytotoxic and helper T cells. DC pick up tumor-associated antigens from diverse sources, process them and present them in both an Major Histocompatibility Complex (MHC) class I and II context to cytotoxic and helper T cells respectively. This has been clearly shown, also for glioma associated antigens from a whole-tumor-cell lysate(5). To date, efficient priming of the patient by dendritic cells implies four sequences of interaction between the dendritic cell and the T cell. Upon binding of the T cell receptor with the MHC complex on the antigen presenting cell displaying the appropriate epitope, a specific activation of the antitumor T cells with high enough avidity for the epitope takes place. Expansion of this T cell clones requires co-stimulatory molecules on the DC. A polarized immune response, preferentially with a Th-1 cytokine profile, should result from the previous interactions. Finally, some indication about the target location should be transferred to the T cells leading to the appropriate T cell homing properties(6-8).

Many rodent models have demonstrated that prophylactic vaccination of mice with tumor-antigen loaded DC can protect immune competent animals from tumor challenge and outgrow. The most relevant experiments are being performed with syngeneic mice-tumor models, to prove the efficacy of the vaccination in an autologous setting underscoring the possibility to break tolerance for self-derived antigens. Moreover, one can raise an anti-tumor immunological memory to make mice survive a re-challenge of cancer cells. More elaborated manipulations of the immune system like e.g. regulatory T cell depletion before vaccination even yield a much stronger protective effect in up to 100% of the exposed animals(9;10). The step towards therapeutic vaccination models, being more relevant for the clinical reality of all day can be made if the crucial timing of inoculation and vaccination is being respected. Probably also due to the aggressive nature of the investigated models, where all mice are dead within 3 weeks after tumor inoculation, it appears crucial to vaccinate the animals not later than one week after the tumor inoculations. After that period, the course of the disease can hardly be influenced, presumably because of the establishment of an efficient immune suppressive, pro-tumor micro-environment around the tumor inocula. This should be understood as the first evidence to use DC vaccinations as an adjuvant therapy in minimal residual disease settings, resembling most the prophylactic setting in which anti-tumor vaccines are so efficient.

3. From proof of the principle to proof of efficacy

Tumor vaccination therapy, even in its more basic form did yield some interesting results in terms of benefit in overall survival in several fields of oncology e.g. renal cell carcinoma, prostate carcinoma, non-small cell lung cancer, colon carcinoma and others(11). Historically, most attention has been paid to so called immunogenic tumors like melanomas. Although proof of the principle has been extensively demonstrated in these tumors using different vaccine approaches and the clinical results obtained until

now are equivalent to standard of care chemotherapy regimens, the final results of immunotherapy in these entities are still modest. Malignant gliomas, the most common primary brain tumors have always been considered to be not suitable for immunotherapy because of their location in the immune privileged central nervous system. To date however, we know that all the obstacles like the blood brain barrier, the lack of lymphatic vessels, the lack of residing antigen presenting cells in the brain, the low MHC expression on the tumor target cells are quite relative. They don't seem to hamper the documented immune responses in patients harboring such tumors(12). To the current understanding the real hurdles in glioma vaccination strategies are the multiple immunosuppressive pathways orchestrated by this type of cancer cells and the lack of universally expressed glioma associated antigens that are really crucial for tumor cell survival. Surprisingly, preliminary data might be pointing to an exploitable lack of spontaneous immunogenicity of malignant gliomas. As such, they develop in a micro-environment protecting them from too extensive immune editing: especially that characteristic could be of major help to try to reset the patients' immunity resulting in a much better immune rejection or control since the original immune-sensitive tumor clones have not yet been eliminated by the natural immune surveillance mechanisms(13).

Immune responses in the brain always elicit some fear for potentially disastrous consequences of an auto-immune attack by the patient's immunity. Unlike vitiligo or even destruction of normal prostate tissue, an auto-immune encephalomyelitis could result in devastating neurological symptoms and deficits. Until now however, no preclinical –other than in a heavily manipulated immune environment- and no clinical data have been published showing any suspicion of serious auto-immunity in the central nervous system, using tumor vaccination strategies. Moreover, numerous phase I and small phase II trials have been published showing the safety and the very attractive low toxicity profile of dendritic cell vaccines in brain cancer. As we're still dealing with a palliative treatment thus far, this perfect patient tolerance profile is highly valuable to build upon for upcoming vaccination strategies. Although today's technology to produce autologous dendritic cell vaccines is still very labour-intensive, it proved to be perfectly feasible to implement it in the daily clinical practice, both in the case of relapsed or newly diagnosed high grade gliomas.

The main criticism against tumor vaccine approaches, often raised till today, comprises the presumed low rate of objective tumor responses. Objective, radiological responses as defined according to RECIST(14) or McDonalds(15) criteria have indeed been developed for radio-and especially chemotherapy regimens during which one aims to reduce the measurable tumor load in the patient. Although they provide valuable information in terms of proof of the principle of the investigated chemotherapy, they should not be considered a synonym for clinically relevant efficacy: in only a few cases, one was really able to demonstrate a clear correlation between objective responses and overall survival benefits(16). More intriguing even is the existence of the so-called 'pseudo-progression' since radiochemotherapy with temozolomid became the standard of care(17). In up to 25% (or even 40%) of cases, one might see an initial increase in radiological tumor volume, rather early after the concomitant radiochemotherapy: strikingly, often especially these patients seem to have a better overall survival chance than the group not displaying these types of misleading radiological changes. Dendritic cell vaccination is known to cause similar radiological images in which transient contrast-enhancements on magnetic

resonance imaging (MRI) might represent inflammatory, vaccine-induced radiological changes that can easily be mistaken for disease progression(18). Although the available literature mentions objective responses in about 13% of vaccinated patients with high grade gliomas, objective responses are not the most appropriate outcome measure for this therapy nor for other experimental therapies. Especially the growing consensus that immunotherapy should be used as an adjuvant treatment for minimal residual disease settings, implies that in many cases there will be no measurable tumor volume at the start of the treatment. Indeed, not all patients today are good candidates to possibly benefit from DC-based immunotherapy. Only tumors amenable to meaningful surgical resections should be considered candidates for adjuvant DC vaccination(19). Several reasons exist for that restriction: first of all one need enough tumor specimen to obtain tumor associated antigens. Secondly, one should be able to stably wean the patient from peri-operative steroids, which might dampen an efficient immune response in case of vaccinations under steroids. Thirdly, by reducing the bulky tumor load, one partially corrects the immune suppressive environment, both locally and systemically, that results from the presence of an organized tumor. In that context, one should mention that modern resection techniques like the use of 5-ALA induced fluorescence guided resections, leading to more extensive glioma resections, can be a complement to the postoperative DC vaccination.

In the past, many researchers have focused on the measurable immune responses in the blood of vaccinated patients as a surrogate endpoint and even as a surrogate of the desired objective clinical responses. The many immunological assays like delayed type hypersensitivity (DTH) reactions – even with skin biopsies of the test sites - , ELISA, ELISPOT, tetramer analysis and diverse in vitro cytotoxicity assays have provided us with valuable insights in relevant immunological mechanisms contributing to the proof of the principle and to our understanding of the complex interaction of the immune system and cancer cells. Regardless the assay used, there seem to be a fairly constant rate of about 50% immune responders in vaccinated cancer patients with malignant gliomas. Apart from a rare exception, most assays failed to correlate with clinical results. We should realize that we have to leave the former linear paradigm stating that cancer vaccines induce a detectable immune response that results in a detectable clinical response (tumor rejection), finally leading to improved overall survival. It did teach us however the important lesson that to date, dendritic cells indeed seem to be the best adjuvants available for clinical use to elicit measurable immune responses in cancer patients, even if almost all of them had been heavily pretreated with radio-and chemotherapy. It has to be mentioned that a rational combination of preferentially, non-myelo-ablative chemotherapy leading to 'pro-inflammatory' immunogenic apoptosis of cancer cells rather synergizes than antagonizes with modern vaccine approaches. Several excellent reviews are dealing with that particular finding(20-22).

Indeed, since recent years a growing consensus on the way to proceed with clinical research in cancer vaccine strategies has arisen. The Cancer Vaccine Clinical Trial Working Group already suggested two parallel tracts of investigation: trials focusing on proof of principle and efficacy trials(23). The former should aim to demonstrate immunological activity, the latter should be designed to show clinical benefit for the patients.

The clinical outcome measures that really do have an impact on the patients' perspectives are overall survival and quality of life. The well tolerated vaccinations often result in a minimal interference with a good quality of life, that is actually only being threatened by disease progression but not substantially by the therapy itself(24). The ambulatory nature of the vaccination schedules further contribute to this low impact on the treatment burden for the individual patient. Especially this low toxicity profile adds to the merits of this therapy in the subgroup of long-term surviving brain cancer patients. Indeed, even more than the possible statistically important impact on median survival data, the substantial group of patients with malignant glioma, both WHO grade III and IV lesions, surviving for many years after vaccination, is the best advocate of this therapeutic approach. Both newly diagnosed, but even more strikingly, relapsed and multi-relapsed patients with high grade gliomas display survival periods of more than 4 to 9 years (manuscript submitted). Considering the classical definition of long-term survivor in the malignant glioma literature, being patients surviving 24 or more months after diagnosis (of primary disease or relapse), substantial numbers of patients, including up to 25% of the relapsed HGG patients undergoing DC vaccination are actually benefitting this opportunity. These long-term survivors are not only an encouragement for this –even not fully mature - immunotherapy approach, but also a source of scientificly important translational knowledge to learn more about the factors predicting this type of outcome after immunotherapy. Final scientific proof of efficacy can of course only be delivered by well-designed, sound randomized controlled trials, several of which are currently running throughout the world.

4. Lack of standards: Disadvantage or opportunity for further improvement?

The 'dendritic cell therapy for cancer'-world today is still characterized by a large variety of similar but not identical approaches. Even the definition of dendritic cell can slightly vary according to their progenitors with different resulting markers on their surface. Although direct harvesting from the peripheral blood is possible, some DC are differentiated out of stem cells or cord blood, but for the vast majority of clinical grade DC today, monocytes are harvested out of the peripheral blood and differentiated into DC. Different culture protocols and conditions result in different phenotypes, but the minimal criteria should be respected before one can claim the cells to be dendritic cells for clinical use: they should display clear cytoplasmic veils, have a high expression of MHC class II molecules as well as co-stimulatory molecules like CD86 and have lost their 'monocyte' markers like CD14. Growing consensus is being reached about the mature DC being the preferred state of the cells to re-inject into the patients, rather than immature cells being able to tolerize rather than immunize the patient. Several maturation cocktails are being used, none of them however have been proven to be superior to the other variants in clinical use, although some evidence exists for the critical involvement of TNFα in the cocktail(25). As the serum of cancer patients might contain identified and unidentified immune suppressive agents inhibiting a good DC differentiation in ex vivo cultures, some favor the use of serum free culture conditions.

Dendritic cells should be loaded with relevant glioma-associated antigens. The sources of these antigens differ widely from well-defined, possibly acid-eluted peptides, proteins, whole tumor cell lysates and homogenates, total tumor RNA, vector constructs, apoptotic

and necrotic bodies. The same lack of data about which source of antigen leads to the most effective vaccine construct is blurring a uniformal approach today. However, many theoretical considerations, could rather support the use of whole tumor cell antigens rather than well-defined single peptides. The most important argument against the exclusive use of a single peptide is the well-established phenomenon of selecting antigen-loss variants of the tumor, leading to an inevitable tumor escape of probably less immune susceptible tumor clones after vaccination. Moreover, the broad repertoire of whole tumor cell derived tumor associated antigens, will lead to presentation of the relevant processed antigens in any type of HLA constitution of the patient, both in an MCH class I and II context. An efficient immunization in these cases is more prone to result in a comprehensive polyclonal T and B cell activation able to provide a better coverage of different tumor clones of the intrinsic heterogenous malignant glioma cells. Nevertheless, further improvements might be expected if a more immunogenic apoptosis pathway could be used to create the source of tumor antigens. Nanoparticles could maybe improve uptake and processing efficiency in the DC and justify further investigation.

Even harder to estimate today, is the optimal use of the appropriate danger signals (PAMP's or pathogen associated molecular patterns or DAMP's being danger associated molecular patterns) to further increase the potency of the vaccine preparation(26). Several candidates, most of them being Toll-like receptor agonists, could substantially potentiate the clinical impact of the dendritic cell-based vaccine. To date, only preliminary data exist to support the use of e.g. imiquimod , poly I:C or clinical grade LPS in the clinical applications of DC vaccines. Several others like ssRNA even have to start being explored for this application. It is evident that with so many parameters being undecided in terms of the most clinically potent DC-based vaccination approach, that a large spectrum of DC-based vaccines result, going from the crude 'dirty' vaccines to the highly elaborated, often genetically engineered cell constructs.

The lack of standards is not only to be found in the vaccine production arm, but even in the target population of patients to treat with DC-based vaccines. Most immunotherapy trials, not only those in brain cancer patients, have been performed in end-stage patients, often heavily pre-treated. Anergic states, either induced by myelo-ablative regimens or by the advanced state of the cancer itself, compromise the theoretical potential of tumor vaccines. Mounting evidence exists nowadays, that DC-based cancer vaccines should be applied to patients with a minimal residual disease status rather than in end-stage cancer patients. Some researchers even advocate the use of cancer vaccines in pre-cancerous lesions, as such referring to the historical prophylactic nature of vaccines and the abundant evidence of the prophylactic efficacy of tumor vaccines in rodent models. In terms of glioma patients, this would imply a shift of the focus to patients with low grade gliomas, as these tumors tend to dedifferentiate over time to secondary high grade gliomas. It would however be very hard, if possible at all in this state of knowledge, to show any survival benefit of this approach in low grade gliomas as the natural course of this condition is so variable that one would need very extensive patient numbers to reach an adequate statistical power in any trial design. Malignant gliomas on the other hand, have the disputable statistical advantage of being rapidly progressive lesions with an almost invariable fatal outcome: a substantial deviation from this natural evolution in vaccinated patients will rapidly result in a broad clinical awareness and possible recognition of the value of cancer vaccines in this setting.

Not only the state of the disease, but also the patient's age and possible timing of vaccination in the course of the treatment are relevant items to consider in the global treatment paradigm using DC-based vaccinations. Indeed, like in many types of oncological treatments, younger age seems to be correlated to a better response and survival after tumor vaccination. This can easily be understood as basic immunological features like thymic involution over time are very likely to influence the potential of active specific immunotherapy approaches in general. As for timing of the implementation of immunotherapy, the question remains whether an upfront integration of the DC-based vaccines in the standard postoperative radiochemotherapy regimen(27) will result in a netto benefit over the alternative approach to apply DC-based tumor vaccination after re-operation for recurrent disease as a single postoperative adjuvant treatment modality without interference of e.g. chemotherapy. Even more basic questions like the best frequency, dose, administration route and boost vaccine frequency and content are unanswered as yet. We do know that in DC-based tumor vaccination, no dose-response, nor dose-toxicity phenomenon is involved, but the optimal 'pharmacological' vaccine characteristics can only be concluded after further comparative clinical data.

Although clinical trials with the current standards of tumor vaccines are mandatory to define the presumed position of cancer immunotherapy in the global oncological treatment regimens, we should realize ourselves that further improvements of the products itself will continue to be made in the next decade. This is of utmost importance to estimate the future potentials of the therapy without losing credits for further innovations of the technology itself.

5. How to learn more? A difficult interplay between the technique, the tumor and the patient

Three main areas of elucidation arise at the moment. First of all, intrinsic improvements of the vaccine details itself are to be monitored by advanced immune monitoring techniques(28). Apart from the classical monitoring assays aimed at detecting a specific anti-tumoral immune response, we should move towards a more global appreciation of the immune system and changes under therapy, both conventional and vaccination therapy. Indeed, preliminary evidence is emerging about the importance of the global immune status of the patient at time of diagnosis and treatment steps. Radiochemotherapy leads to a 're-setting' of the patient's immune system, possibly already then priming it towards a favorable or unfavorable starting position for subsequent immunotherapy. The vaccine itself might cause quantitative and qualitative shifts in immune cell subtypes, not only regulatory or effector T cells, but also natural killer cells or natural killer T cells. We should start to include monitoring of local immune cells in the target environment, i.e. the brain and brain tumor micro-environment, rather than only in the blood, which is often not (at all) correlating with the local immune conditions in the target organs. Probably coinciding with shifts in cellular compartments of the immune system, cytokine environments might mimic the underlying changes and are good candidates to represent relevant switches in micro-environment facilitating or suppressing an effective tumor rejection by the immune system. Usually, a Th-1 pro-inflammatory environment is believed to be beneficial for tumor rejection, although other

types of cytokine profiles, like e.g. a Th-17 mediated immune response are gaining importance in the global picture. Moreover, a TLR-agonist matured, fully Th-1 polarized DC vaccine has not yet been applied in larger clinical trials. A pro-inflammatory environment however is only facilitating a tumor rejection, if there's no evolution to a chronic inflammatory state, like in chronic inflammatory diseases : in this particular situation indeed, the immune system exhibits important signs of immune exhaustion. Even this state can be detected and monitored to date in an increasingly accurate way e.g. by analyzing zeta-chain down regulation in the T cell compartments(29). Many other relevant cell types from tumor infiltrating macrophages (especially those with pro-tumor 'M2' phenotype – called 'alternatively activated macrophages'), or tumor infiltrating myeloid-derived suppressor cells (MDSC), both abundantly present in several glioma models and human glioma specimens are only beginning to be unraveled. Analogue to the regulatory T cell compartment, which has been recognized for years as a relevant player in the balance between tumor rejection and immune tolerance, the first preliminary reports arise about 'regulatory dendritic cells'. It goes without saying that the fast acquisition of growing knowledge on the complex interplay between all these immune cells will influence our future understanding and concept of the current vaccine approaches.

A second important source of contributing insights will come from the molecular analysis of the tumor specimens. The molecular profile of a malignant glioma with the characterization of MGMT promotor methylation status, 1p19q co-deletion, PTEN loss, IDH1 mutation etc is rapidly gaining access to the routine clinical assessment of a common high grade glioma. To the same extent, predictive (or prognostic) markers for immunotherapy will become available as there are already now the reports on tumoral HOX genes relevant for 'immune reactions' (30)or the suggestion of an 'immunotherapy prone' mesenchymal phenotype of the glioblastoma tumor cells(31).

A third emerging field is the 'predictive' radiology field. In era's of pseudo-progression and therapy-induced radiological changes on gadolinium(Gd)-enhanced MRI of the brain tumor patients, distinctive radiological techniques predicting a tumor response or a tumor progression are of utmost importance. Especially its non-invasive character turns MRI into a preferred monitoring tool for malignant glioma follow-up especially for the new therapy classes. Preliminary steps are being made to try to distinguish vaccine-induced radiological changes from tumor progression in Gd-enhancing lesions on the MRI, using perfusion-weighted (regional cerebral blood volume-rCBV) and diffusion-weighted (apparent diffusion coefficient-ADC) images in combination with spectroscopic findings(18). In terms of correct patient counseling, these new monitoring paradigms are considered crucial for the near future.

6. How to proceed?

It is clear that we're at a crucial step in the decision to move on with immunotherapy or not. Therefore we should acknowledge the particular difficulty to find a balance between gaining the appropriate clinical evidence that immunotherapy adds to the favorable outcome of the patients with high grade gliomas on the one hand and creating a stimulating environment for further optimalisation of an as yet immature technology on the other hand.

A too quick global 'dissemination' of today's technologies will probably kill the credits for further development as too many aspects of the tumor vaccine approach itself are rapidly evolving towards a theoretical optimum.

The combination of both objectives can be accomplished by performing further preclinical experiments and small-scale early-clinical trials to optimize the vaccine technology as such and a gradual implementation of solid techniques of DC-based vaccine production and administration in large, randomized trials with the appropriate control arms to stepwise introduce the best available DC vaccine at that moment. The latter element is imperfect in se, but nevertheless highly required, even already at the moment, given the unmet medical need and the promising results for important subgroups of patients thus far.

It is hard to predict the outline of the final, optimal DC-based vaccine for the future. Nevertheless it is clear it will have to integrate all the aspects of the difficult interplay between the technique, the tumor and the patient. Indeed, all of these three elements are highly relevant for a successful immunotherapy approach and probably for any approach at all. As for the anti-glioma DC-based vaccine production itself, preliminary evidence is being reported that whole tumor cell –based preparations are superior to defined epitopes in terms of overall survival data. Which types of other therapies that might synergize the most with cancer vaccines is subject of further investigations. Many candidates from radio-and chemotherapy over anti-angiogenesis, blood-brain barrier disruption techniques or oncolytic virus therapy do exist or are emerging today. Immune modulators and strategies able to modify the tumor micro-environment will play a crucial role in the future cancer vaccines. For anti-glioma vaccines, again many candidates immune modulators are at the edge of a clinical application to improve the overall vaccine efficiency. Substances like galectin-1, transforming growth factor β, interleukin 10, interleukin 6 and vascular endothelial growth factor are known to hamper vaccine efficiency and might even be interconnected, so interference with either of these locally secreted factors could result in a dramaticly increased vaccine efficacy. Finally, the patient itself creates the background that might alter the impact of all the interventions according to pre-existing parameters. In that regard, the notion of inherent immune cycles is an intriguing finding that needs however further clarification. Nevertheless, it might explain the indirect evidence we have for the tremendous importance of the timing of immunotherapy interventions on the final outcome of the patient.

All this implies that we should consequently move into the direction of 'individualized' or 'customized' cancer vaccines rather than mass-produced 'off the shelf' constructs. Therefore , we should not mix up the ideal medical tracts with the desired 'manufacturing profile' of a cancer vaccine. It is highly likely that clinical results in this area of research will proceed the elucidation of all the underlying mechanisms rather than vice versa. Also for regulating agencies of cellular therapies, all the above mentioned aspects hold an enormous challenge but also a 'life-important' responsibility.

7. References

[1] Weller RO, Engelhardt B, Phillips MJ. Lymphocyte targeting of the central nervous system: a review of afferent and efferent CNS-immune pathways. Brain Pathol 1996; 6(3):275-288.

[2] De Vleeschouwer S, Van Gool SW, Van Calenbergh F. Immunotherapy for malignant gliomas: emphasis on strategies of active specific immunotherapy using autologous dendritic cells. Childs Nerv Syst 2005; 21:7-18.

[3] Steinman RM. The dendritic cell system and its role in immunogenicity. Annu Rev Immunol 1991; 9:271-296.

[4] Steinman RM, Mellman I. Immunotherapy: bewitched, bothered, and bewildered no more. Science 2004; 305:197-200.

[5] De Vleeschouwer S, Arredouani M, Ade M, Cadot P, Vermassen E, Ceuppens JL et al. Uptake and presentation of malignant glioma tumor cell lysates by monocyte-derived dendritic cells. Cancer Immunol Immunother 2005; 54:372-382.

[6] Gilboa E. DC-based cancer vaccines. J Clin Invest 2007; 117(5):1195-1203.

[7] Kalinski P, Hilkens CMU, Wierenga EA, Kapsenberg ML. T-cell priming by type-1 and type-2 polarized dendritic cells: the concept of a third signal. Immunol Today 1999; 20:561-567.

[8] Kalinski P, Urban J, Narang R, Berk E, Wieckowski E, Muthuswamy R. Dendritic cell-based therapeutic cancer vaccines: what we have and what we need. Future Oncol 2009; 5(3):379-390.

[9] Maes W, Galicia Rosas G, Verbinnen B, Boon L, De Vleeschouwer S, Ceuppens JL et al. DC vaccination with anti-CD25 treatment leads to long-term immunity against experimental glioma. Neuro-oncol 2009; 11(5):529-542.

[10] Maes W, Van Gool SW. Experimental immunotherapy for malignant glioma: lessons from two decades of research in the GL261 model. Cancer Immunol Immunother 2011; 60(2):153-160.

[11] Mocellin S, Rossi CR, Lise M, Marincola FM. Adjuvant immunotherapy for solid tumors: from promise to clinical application. Cancer Immunol Immunother 2002; 51(11-12):583-595.

[12] Dunn GP, Dunn IF, Curry WT. Focus on TILs: Prognostic significance of tumor infiltrating lymphocytes in human glioma. Cancer Immun 2007; 7:12.

[13] Van Gool SW, Maes W, Ardon H, Verschuere T, Van Cauter S, De Vleeschouwer S. Dendritic cell therapy of high grade gliomas. Brain Pathol 2009; 19:694-712.

[14] Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000; 92(3):205-16.

[15] Macdonald DR, Cascino TL, Schold SC, Jr., Cairncross JG. Response criteria for phase II studies of supratentorial malignant glioma.
J Clin Oncol 1990; 8(7):1277-1280.

[16] De Vleeschouwer S, Rapp M, Sorg RV, Steiger HJ, Stummer W, Van Gool S et al. Dendritic cell vaccination in patients with malignant gliomas: current status and future directions. Neurosurgery 2006; 59(5):988-999.

[17] Taal W, Brandsma D, de Bruin HG, Bromberg JE, Swaak-Kragten AT, Smitt PA et al. Incidence of early pseudo-progression in a cohort of malignant glioma patients treated with chemoirradiation with temozolomide.

Cancer 2008; 113(2):405-410.

[18] Vrabec M, Van Cauter S, Himmelreich U, Van Gool SW, Sunaert S, De Vleeschouwer S et al. MR perfusion and diffusion imaging in the follow-up of recurrent glioblastoma treated with dendritic cell immunotherapy: a pilot study. Neuroradiology 2010.

[19] Rutkowski S, De Vleeschouwer S, Kaempgen E, Wolff JEA, Kuhl J, Demaerel P et al. Surgery and adjuvant dendritic cell-based tumour vaccination for patients with relapsed malignant glioma, a feasibility study.
Br J Cancer 2004; 91:1656-1662.

[20] Masucci GV, Mansson-Brahme E, Ragnarsson-Olding B, Nilsson B, Wagenius G, Hansson J. Alternating chemo-immunotherapy with temozolomide and low-dose interleukin-2 in patients with metastatic melanoma. Melanoma Res 2006; 16(4):357-363.

[21] Nowak AK, Robinson BW, Lake RA. Synergy between chemotherapy and immunotherapy in the treatment of established murine solid tumors. Cancer Res 2003; 63(15):4490-4496.

[22] van der Most RG, Currie A, Robinson BW, Lake RA. Cranking the immunologic engine with chemotherapy: using context to drive tumor antigen cross-presentation towards useful antitumor immunity. Cancer Res 2006; 66(2):601-604.

[23] Hoos A, Parmiani G, Hege K, Sznol M, Loibner H, Eggermont A et al. A clinical development paradigm for cancer vaccines and related biologics. J Immunother 2007; 30(1):1-15.

[24] De Vleeschouwer S, Fieuws S, Rutkowski S, Van Calenbergh F, Van Loon J, Goffin J et al. Postoperative adjuvant dendritic cell-based immunotherapy in patients with relapsed glioblastoma multiforme. Clin Cancer Res 2008; 14(10): 3098-3104.

[25] McIlroy D, Gregoire M. Optimizing dendritic cell-based anticancer immunotherapy: maturation state does have clinical impact. Cancer Immunol Immunother 2003; 52(10):583-591.

[26] Koski GK, Cohen PA, Roses RE, Xu S, Czerniecki BJ. Reengineering dendritic cell-based anti-cancer vaccines. Immunol Rev 2008; 222:256-76.:256-276.

[27] Ardon H, Van Gool S, Lopes IS, Maes W, Sciot R, Wilms G et al. Integration of autologous dendritic cell-based immunotherapy in the primary treatment for patients with newly diagnosed glioblastoma multiforme: a pilot study. J Neurooncol 2010.

[28] Jian B, Yang I, Parsa AT. Monitoring immune responses after glioma vaccine immunotherapy. Neurosurg Clin N Am 2010; 21(1):195-199.

[29] Baniyash M. Chronic inflammation, immunosuppression and cancer: new insights and outlook. Semin Cancer Biol 2006; 16(1):80-88.

[30] Murat A, Migliavacca E, Gorlia T, Lambiv WL, Shay T, Hamou MF et al. Stem cell-related "self-renewal" signature and high epidermal growth factor receptor expression associated with resistance to concomitant chemoradiotherapy in glioblastoma.
J Clin Oncol 2008; %20;26(18):3015-3024.

[31] Prins RM, Soto H, Konkankit V, Odesa SK, Eskin A, Yong WH et al. Gene expression profile correlates with T-cell infiltration and relative survival in glioblastoma patients vaccinated with dendritic cell immunotherapy. Clin Cancer Res 2011; 17(6):1603-1615.
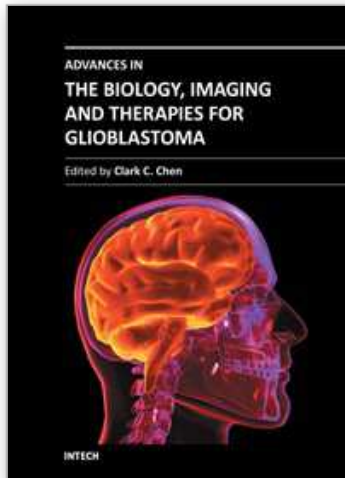
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