Editorial Commentary

# Dendritic cell vaccination for glioblastoma multiforme patients: has a new milestone been reached?

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On November 17th, 2022, the first phase III study on dendritic cell (DC) vaccination for glioblastoma multiforme (GBM) patients was published (1), of which an earlier report came out in 2018 (2). Does this represent a new milestone in the development of active specific immunotherapy towards GBM treatment?

GBM is the most frequent primary malignant brain tumor in adults, with an incidence of four to five new patients per 100,000 adults per year. Despite being an orphan disease, community burden in terms of years of life lost is highest of all cancer types. Treatment with the current standard of care (SoC) of neurosurgery, followed by radiochemotherapy and finally maintenance chemotherapy with Temozolomide (TMZm) is usually not curative, and heavily weigh on the health-related quality of life. The need for innovative new treatments lead to current advances in anti-angiogenesis, targeted therapies, innovative radiotherapy techniques, and nanotechnologies. Physics-based treatments like tumor treating fields (TTF) (3) or modulated electrohyperthermia (mEHT) (4), and treatments with oncolytic viruses (OVs) (5) have already been implemented in clinical application. The exciting but extremely complex domain of immunotherapy in oncology was honoured with two Nobel prizes in the last decade (2011: Beutler, Hoffmann, Steinman; 2018: Honjo, Allison), and was nominated "Breakthrough in Cancer Treatment" in 2013. The term "immunotherapy" includes several distinctive modes: restorative, adoptive, passive, immunogenic cell death (ICD), modulatory and active-specific immunotherapy, the latter representing anti-cancer vaccines. Personalized combinations of immunotherapies are called individualized multimodal immunotherapy (IMI). IMI supplements anti-GBM treatment strategies together with neurosurgery, radiochemotherapy and chemotherapy.

Anti-cancer vaccines are medicinal products aimed to elicit an immune response within the body against one or more tumor antigens. Three components make a vaccine effective: the antigen, the carrier and the danger signal. Each component is prone to variability. Antigens can be specific, or non-specific as they can be derived from whole tumor cells, tumor lysates, peptides, RNA or DNA. The vehicle can be a simple solution, strengthened with danger signals such as poly I:C, montanide, or granulocyte-macrophage colony-stimulating factor (GM-CSF). Imiquimod can be applied to the skin to elicit additional danger signals. If an autologous (rarely allogeneic) DC vehicle is used, these can eventually be matured *ex vivo* in the presence of cytokines and/or Toll-like receptor agonists, which deliver danger signals. Notwithstanding its complexity, conceptualization

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of how to culture human DCs (6) to world-wide first clinical application to treat a GBM patient (7), of note by the same author as the paper commented here, took merely 6 years. At that time, innovation was less hindered by regulation.

From this first report (7) till March 2023, 77 studies were published about DC vaccination for patients with malignant glioma, including two studies in the domain of diffuse intrinsic pontine glioma. In six meta-analyses, the significant improvement in overall survival (OS) due to DC vaccines has been demonstrated (8-13), of note without significant adverse events (12). Almost all studies were phase I, phase I/II or phase II trials. The further development of DC vaccination into larger randomized controlled trials (RCT) appeared to be a big hurdle with several medical and non-medical challenges (14).

Like a few other trial initiatives at that time (15), the study discussed here was originally designed as a phase IIb RCT with an experimental arm being SoC plus DC vaccination versus SoC plus placebo, and progression-free survival (PFS) as primary endpoint. At time of relapse, both the experimental arm and the placebo arm continued or started with DCVax®-L to secure the OS benefit. In the current phase III report of the data obtained along the phase IIb randomization, the OS, originally a secondary read-out, became the primary endpoint as PFS was deemed too challenging to monitor reliably. An external control arm (ECA) was designed on the basis of reported control groups in contemporary and closely matched RCTs in literature, both for patients with newly diagnosed as for relapsed GBM. Because of lack of individual patient data, a matching-adjusted-indirect-comparison (MAIC) analysis was used. Regulatory techniques were used to change the read-out and trial design, aiming to preserve the good clinical practice label of the trial. So, we end up with a phase III prospective non-randomized externally controlled cohort trial of randomized patients in a phase IIb cross-over study design. The fact that the patients were recruited and "prospectively" analyzed for OS, and an ECA was created, still allowed the term "trial".

The published work reportedly faced many challenges.

(I) The insertion of DC vaccination into the first-line combined treatment for GBM is difficult. Almost all researchers started with DC vaccination shortly after the radiochemotherapy, during the maintenance chemotherapy. Several arguments were discussed to support this combination (16). The effect of chemotherapy for immunization, however, appears to be unequivocal (17). DC vaccination after TMZm instead of during TMZm resulted in slightly better 2-year OS (15). It is therefore likely that DCVax®-L will work better after TMZm to improve OS. At least the Hazard ratio, here reflecting the relative risk for mortality in comparison to the ECA, was stronger reduced (0.58) in the patients with recurrent GBM receiving DCVax®-L, as compared to the Hazard risk reduction (0.8) upon DCVax®-L treatment in the newly diagnosed patients under chemotherapy, suggesting that DCVax®-L might be more effective in patients outside chemotherapy.

(II) The MGMT promoter methylation status emerges as a strong prognostic factor. Clinical risk factors, molecular risk factors, risk factors within the tumor-host interaction and even the systemic immune system all influence the ultimate prognosis, making RCT designs extremely complex (14). The trial data showed improved OS in patients receiving DCVax®-L for both newly diagnosed patients and relapsed patients (including the cross-over group). However, subgroup analysis showed that OS improvement only occurred in patients with MGMT promoter-methylated GBM. The lack of improvement in the MGMT promoter-unmethylated GBM patients remains a concern.

(III) The authors acknowledged explicitly the difficulty of PFS as endpoint for the randomized question. It proved difficult to reliably distinguish actual disease progression from pseudo-progression comprised of inflammation or necrosis, or from vaccine-induced infiltration of immune cells. There are many clinical endpoints in oncology and immunotherapy (18). In general, instead of PFS, OS is the most important read-out. However, using OS as primary endpoint requires different statistical analyses. For this study (1), some issues are under discussion. (i) In the original study design, the primary endpoint was PFS and one of the secondary endpoints was OS, which theoretically can only be captured after the primary endpoint. Only by designing a completely new trial, the OS could gain enough weight as phase III-level information to assess the treatment outcome. (ii) The matching with the ECA can be considered as a weakness, but was performed by an independent third-party organization using pre-specified matching criteria and state of the art methodologies. (iii) Finally, the inclusion and randomization were placed about 3 months after surgery. This is a time window in which already about one fifth to one fourth of patients might become progressive again. The study explicitly mentions that patients having radiographic evidence of early disease progression following radiochemotherapy were excluded for randomization. Those type of patients, however, were included in the studies that delivered the ECA. Therefore, we have to conclude that patients with worse prognosis were present in the OS data of the ECA, but were not present in the OS

 

data of this study. Nevertheless, the authors specifically conducted a sensitivity analysis precisely to address this critical point (1). In the sixth sensitivity analysis, published in the supplements, two of the five comparator studies were dropped because it was not clear whether they had excluded patients with early progression, and the HR remained the same (0.8). This demonstrates that the authors recognized the potential of early progression to influence the OS, and addressed it appropriately. The results showed that at least in this study there was no effect from this potentially confounding factor, making the improvement of OS due to DCVax®-L reliable. Moreover, the significant OS data and strong hazard ratio observed in the relapsed patients and their matched ECA might have the strongest value and might be most meaningful to demonstrate efficacy of DCVax®-L.

(IV) Patient-specific dynamics within the tumor (change in tumor mutational burden, change in antigenicity under selective treatments), the tumor-host interaction and the systemic immune compartment, partially influenced by radiotherapy, chemotherapy and steroids, influence the OS in study populations within an RCT (14). The compared OS obtained between protocols in an RCT or with an ECA, might be influenced more by different kinetics in patient-specific dynamics than by the anticancer effects of the protocol intervention. This is a general problem for all RCTs in highly dynamic tumors. The clinical research methodology fails when highly dynamic tumors in a highly dynamic (micro-)environment are forced to be treated with Good Clinical Practice-approved but fixed treatment protocols.

(V) The rapid gain of knowledge in immuno-oncology means that "out-dated" advanced therapy medicinal products (ATMPs) must be tested over far too long trial periods in patients, thereby blocking translation of latest insights in immuno-oncology. Autologous tumor antigens must be presented to the immune system in the presence of danger signals. To realize this in the context of autologous DC vaccines, *ex vivo* maturation of DCs after loading with tumor antigens is critical. The first patient inclusion in this trial was in 2007. Most likely, fixed standardized DCVax®-L production processes were used during the complete trial, even though improved methods for DC production emerged in the meantime. In earlier publications by this group, no maturation step is described at the end of DC differentiation and antigen-loading. Also, in the clinical reports (1,2), it is not mentioned whether immature or mature DCs were used. It is thus unclear whether maximal vaccine potency was reached with appropriate maturation signals at the end of the DCVax®-L product development. First reports on the use of mature DCs for vaccination in GBM patients were released only in 2004 (19,20) and 2007 (21,22), hence at the time the company finalized the developmental phase to bring the product DCVax®-L into industry-driven clinical trials.

(VI) The massive increase of regulations for the production of ATMPs and conduction of clinical trials decreased clinical trial initiatives and increased costs for clinical research, reducing access to innovative treatments for patients. Although patient recruitment was initiated in 2007, it had to be paused from 2009 to 2011 for economic reasons. The midpoint of enrollment was reached in May 2014, and the final patient was enrolled in November 2015 (2). The conclusion that the primary endpoint was impossible to analyze was published in November 2022 (1). It shows how difficult it must have been to bring all the work into a sound scientific report that serves the scientific community for further development of DC vaccination for GBM patients.

(VII) Finally, the recruitment of "only" 331 patients over about 5 years in more than 90 large neuro-oncology clinics inevitably suggests a large patient selection for participation in the trial. All traditional clinical trials require clear and multiple eligibility criteria to ensure that the study population is similar in all baseline factors that may affect the potential benefits and risks from the intervention being studied. This not only requires large study populations, with a tendency to get bigger and larger, but it also implies that patients that may be at greater risk of adverse events from the trial and those who are not expected to benefit, will be excluded. While this all makes sense to eliminate bias and balances for unknown covariates, it is argued that overly strict eligibility criteria (i) result in lower patient accrual, which already is a challenge for rare diseases where the sample sizes are small; (ii) result in increased length, complexity and costs; and (iii) can ultimately lead to trial results to be less generalizable. For GBM patients, high level clinical research evidence of efficacy of an intervention is usually generated via a highly selected minority of patients (23), resulting in study populations to be unrepresentative of the clinical population of patients. The current and generally accepted clinical research methodology limits patient access to new treatments. It also creates a gap between clinical research "efficacy" and medical "effectiveness", the latter comprising of many and more complex elements, in a real-world GBM population.

Can the scientific community consider this publication (1) as a new milestone in the development of DC vaccination as active specific immunotherapy, aimed to improve the OS of

 

patients with GBM? The answer is definitively yes. It is the first phase III controlled report that shows an improvement of the OS in patients with GBM. For the first time, a level I of clinical research evidence in evidence-based medicine is reached, and extends the level IIa clinical research evidence already observed with systematic reviews of phase I or II clinical trials (8-13).

On top of that, a particular observation was the very good outcome of patients treated with DCVax®-L at time of relapse plus TTF (1). The mode of action of TTF relies at least in part on an ICD immunotherapy effect (24). This finding illustrates the potential of multimodal immunotherapy, and offers perspectives for smart combination therapies for GBM patients in consecutive phases, which we have developed (25). (I) In our own approach, we have placed IO-Vac® DC vaccination not during but after the TMZm period, instead strengthening this first anti-cancer phase of TMZm monotherapy with ICD immunotherapy with OVs (Newcastle Disease Virus) and sessions of mEHT. (II) After chemotherapy, an immunization phase with IO-Vac® DC vaccination is scheduled, in combination with individualized modulatory immunotherapies (checkpoint inhibitors, anti-histamine receptor 1 drugs, Risedronate, metronomic cyclophosphamide, metronomic capecitabine, curcumin, and/or celecoxib). (III) Finally, continued repetitive ICD immunotherapy courses and boost IO-Vac® combined with individualized modulatory immunotherapies aim to maintain and broaden the immune protection. Real-world OS data obtained with such multiphase combined treatment strategy, including IMI in each phase of treatment, give realistic hope to obtain a better control over GBM with clear improvement of OS and maintaining good health-related quality of life (25). Administration of DC vaccination should be part of IMI within a multiphase combined medical treatment to be conducted by specialized immuno-(neuro-)oncologists who are able to assess the oncologic and immune status of each individual patient and guide the patient through all dynamic changes within the tumor and the host. Leading immuno-oncology centres should translate rapidly evolving knowledge from science into individualized patient treatment planning and deliver data to the scientific and medical community. Therefore, all pieces of knowledge (1,25) are of high value and pave the way to integrate innovative immunotherapy modalities as an approved and community-supported component of the multiphase combined medical treatment for patients with GBM. Winning each day of life with good quality of life in patients with GBM is invaluable in itself.

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