European Journal of Cancer 113 (2019) 41–44

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Current Perspective

Combining conventional therapy with immunotherapy: A risky business?

A. Coosemans [a,b], A. Vankerckhoven [b], T. Baert [b,c], L. Boon [d], H. Ruts [b], M. Riva [b], S. Blagden [e], M. Delforge [f], N. Concin [g], M.R. Mirza [h], J.A. Ledermann [i], A. du Bois [c], I. Vergote [a,b,j,*]

[a] *Department of Gynaecology and Obstetrics, Leuven Cancer Institute, UZ Leuven, Leuven, Belgium*
[b] *Department of Oncology, Laboratory of Tumour Immunology and Immunotherapy, ImmunOvar Research Group, KU Leuven, Leuven, Belgium*
[c] *Kliniken Essen Mitte (KEM), Department of Gynaecology and Gynaecologic Oncology, Essen, Germany*
[d] *Bioceros BV, Utrecht, the Netherlands*
[e] *Early Phase Clinical Trials Unit, Department of Oncology, University of Oxford, United Kingdom*
[f] *Department of Haematology, Leuven Cancer Institute, UZ Leuven, Leuven, Belgium*
[g] *Department of Gynaecology and Obstetrics, Medizinische Universität Innsbruck, Innsbruck, Austria*
[h] *Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark*
[i] *UCL Cancer Institute, University College London, London, United Kingdom*
[j] *Department of Oncology, Laboratory of Gynecologic Oncology, KU Leuven, Leuven, Belgium*

Received 8 February 2019; accepted 27 February 2019
Available online 6 April 2019

KEYWORDS
Immunotherapy;
Tumor immunology;
Chemotherapy;
Combination;
Survival

Abstract Because of the failure of immunotherapy as single agent in a number of cancers, current clinical trials are focusing on combining immunotherapy with other therapies. The most frequently chosen combination for immunotherapy is chemotherapy. However, almost no preclinical data on this combination is available. Some studies even showed a dismal effect of combining chemotherapy with immunotherapy. Taken into account that each of the therapies chosen in a combination will influence the cancer cells but also immune effector cells as well as immunosuppressive cells, and that these three partners will also interact with each other, launching a combination to the patient without proper immune monitoring and preclinical evidence might be devastating.

* *Corresponding author*: UZ Leuven, Department of Gynaecology and Obstetrics, Herestraat 49, 3000 Leuven, Belgium.
E-mail addresses: an.coosemans@kuleuven.be (A. Coosemans), ann.vankerckhoven@kuleuven.be (A. Vankerckhoven), T.Baert@kliniken-essen-mitte.de (T. Baert), l.boon@bioceros.com (L. Boon), hanne.ruts@hotmail.com (H. Ruts), matteo.riva@kuleuven.be (M. Riva), sarah.blagden@oncology.ox.ac.uk (S. Blagden), michel.delforge@uzleuven.be (M. Delforge), nicole.concin@i-med.ac.at (N. Concin), Mansoor.Raza.Mirza@regionh.dk (M.R. Mirza), j.ledermann@ucl.ac.uk (J.A. Ledermann), prof.dubois@googlemail.com (A. du Bois), Ignace.vergote@uzleuven.be (I. Vergote).

https://doi.org/10.1016/j.ejca.2019.02.014
0959-8049/

The immune system is now known to play a pivotal role in the onset and development of cancer [1,2]. The adaptive and innate immune responses are mobilized to eliminate neoplastic cells as they emerge. In some cases, elimination is not entirely successful and an equilibrium phase is established whereby the neoplastic cells enter a dormant state, side by side with the immune system. During this process, tumour cells can be edited and consequently escape this immunological control. Eventually, the immune system fails, and uncontrolled tumour proliferation occurs. Tumours themselves and/or through their interaction with the microenvironment may attract immunosuppressive cells, such as MDSC (myeloid derived suppressor cells, Treg (regulatory T cells), M2 macrophages and others, to divert immune detection and facilitate unregulated tumour growth. Immunological evasion arises in all tumours, but the key players establishing the immune suppressive microenvironment are different per tumour, maybe even for different stages of the disease. A detailed understanding of these tumour-specific processes is gradually emerging [3], and it is essential to be aware of these as anticancer immunotherapy will change this environment. Failure or discontinuation of numerous clinical trials has highlighted the importance of such knowledge. Immune checkpoint inhibitors have shown limited activity in the majority of tumours and can even create accelerated cancer progression, or unexpected toxicities, when combined with other immunomodulatory drugs. This was the case with pembrolizumab, a monoclonal antibody against programmed death receptor-1 (anti-PD1), in multiple myeloma (KEYNOTE 183 [NCT02576977] and KEYNOTE 185 [NCT02579863]) and also in adult T-cell leukemia–lymphoma [4]. Based on two recent publications in *Nature Medicine*, it is reassuring to note that efforts are currently underway to predict sensitivity and response to immune-oncology (IO) agents before their initiation [5,6]. To add complexity, there is increasing evidence that conventional treatments (chemotherapy [7–9], radiotherapy [10] and surgery [11]) also have an impact on the immune system (Fig. 1). This re-enforces the importance of evaluating the immune status before commencing IO-containing combinations. Notwithstanding this lack of information, a recent review by Brown *et al.* [8] revealed that more than 200 ongoing or planned clinical trials are registered in which IO agents are combined with chemotherapy.

This is occurring despite a lack of preclinical data to justify the choice of combinatorial agents. Some clinical trials have shown a better outcome when chemotherapy and immune checkpoint inhibitors are administered sequentially rather than concomitantly [12]; in other studies, the administration of chemotherapy after initiation of immune checkpoint inhibitors was beneficial [13]. Recently, the JAVELIN Ovarian 100 and 200 (NCT02718417 and NCT02580058, respectively) (combining anti-PDL1 with chemotherapy in ovarian

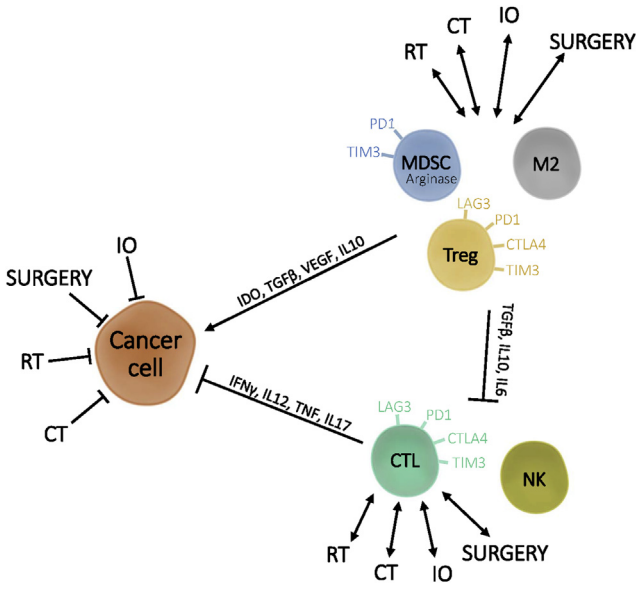

Fig. 1. Complex interplay between conventional therapies, immune-oncology agents, cancer cells and immune cells. Abbreviations: radiotherapy (RT), chemotherapy (CT), immune-oncology agents (IO), Indoleamine 2,3-dioxygenase (IDO), tumour growth factor (TGF), vascular endothelial growth factor (VEGF), interleukin (IL), interferon (IFN), tumour necrosis factor (TNF), cytotoxic T cell (CTL), programmed cell death 1 (PD1), cytotoxic T-lymphocyte associated protein 4 (CTLA4), T-cell immunoglobulin and mucin-domain containing-3 (TIM3), lymphocyte-activation gene 3 (LAG3), myeloid derived suppressor cell (MDSC), regulatory T cell (Treg), macrophage type 2 (M2).

cancer) were prematurely stopped because no significant differences in survival were obtained compared with chemotherapy in monotherapy [14,15]. Caution is needed for a possible devastating effect of combining chemotherapy with IO agents. As we have insufficient knowledge about the immune status of a patient at therapy initiation, incorrect sequencing of chemotherapy and IO agents could shorten survival. This was reported ten years ago in a first-line chemotherapy study in ovarian cancer. Carboplatin and paclitaxel were administered alone or in combination with interferon gamma 1b (IFNγ1b). The study was stopped prematurely because a significantly shorter overall survival was observed in the IO-containing arm ($p = 0.001$). The authors only hypothesized about the cause (direct toxicity of IFNγ1b, toxicity on bone marrow, leading to therapy reduction or an increase in Treg); however no immune monitoring was performed [16].

As an example, we refer to our own experience with the ID8-fLuc serous ovarian cancer mouse model [17]. We observed a shortened overall survival depending on the sequence of immunotherapy and chemotherapy (Fig. 2). In the first experiment (A), dendritic cell immunotherapy was combined with carboplatin-gemcitabine; in the second (B), an anti-PD1 was combined with carboplatin-paclitaxel and

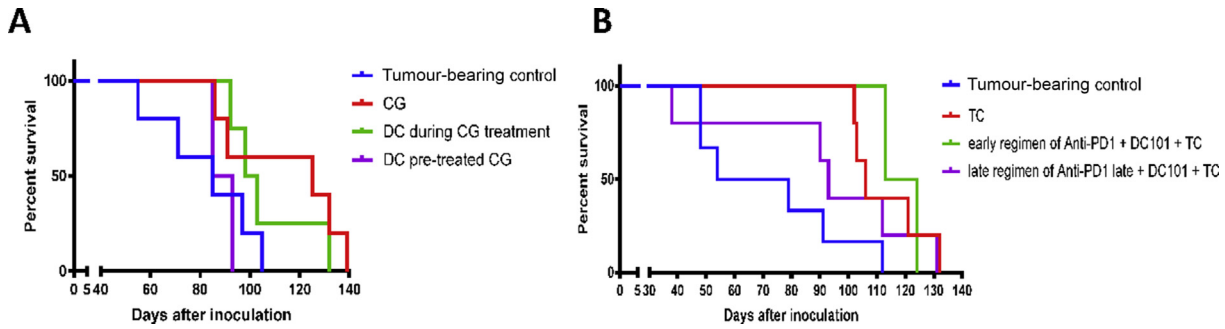

Fig. 2. Kaplan–Meier survival curves on combinatorial therapies, administered in the ID8-fLuc ovarian cancer mouse model. **A.** The red curve represents mice receiving carboplatin-gemcitabine (CG) only, given intraperitoneally at day 21 and day 35 after tumour inoculation (n = 5). Dendritic cell (DC) immunotherapy was given subcutaneously at day 27, 34 and 41 after tumour inoculation (n = 4, 1 toxicity death) (green curve) (median survival 100.5 days). The purple curve represents mice receiving DC immunotherapy at day 1, 7 and 14 after tumour inoculation (n = 2, 3 toxicity deaths) (median survival 89 days). The blue curve represents tumour bearing controls, receiving no therapy (n = 5). **B.** The red curve represents the group of mice receiving only carboplatin-paclitaxel (TC), given intraperiteonally at day 21 and day 35 after tumour inoculation (n = 5, 1 toxicity death). The green and purple curve represent the mice receiving anti-PD1 (Clone RPM1-14, Bioceros BV, The Netherlands), DC101 (anti-VEGFR2) (1 mg/kg, 2 times per week, starting from day 20) and chemotherapy with administration of anti-PD1 in an early regimen (day 20–22–24–26–28 after tumour inoculation) in case of the green curve (n = 2; 4 toxicity deaths) (median survival 118.5 days) and in a late regimen (day 30–32–34–36–38 after tumour inoculation) in case of the purple curve (n = 5, 1 toxicity death) (median survival 93 days). As in figure A, blue represent the untreated tumour bearing mice (n = 6) (median survival 66.5 days). All murine experiments were performed in female mice, according to the EU directive 2010/63/EU and the ARRIVE guidelines.

an angiogenic inhibitor (DC101). The positive effects of synergistic administration (green curve experiment B) might be explained by the finding that PD-L1 expression tends to increase shortly after chemotherapy [18,19].

Shifts in immune cell composition induced by the different therapies separately or together should be considered as the cause of failure or success of combinations. This information can only be obtained by thorough preclinical work, investment in immune monitoring and assays that detect early response. Until we have that knowledge, we need to be careful in choosing the order, timing and dosage of combination therapies [9,20]. Inconsiderate decision-making can result in an accidently chosen beneficial combination without understanding the underlying mechanistic reason, or it can lead to a therapeutic failure with either a similar or, of greater concern, worse outcome.

Conflict of interest statement

AdB (no direct COI but some relations to companies dealing with oncology products in general).

Funding

This work was supported by the Olivia Fund [grant number 2017/LUF/00135 to A.C.] and the Amgen Chair for Therapeutic Advances in Ovarian Cancer [grant number 2017/LUF/00069 to I.V.]. JAL is a NIHR Senior Investigator.

References

[1] Schreiber RD, Old LJ, Smyth MJ. Cancer immunoediting: integrating immunity's roles in cancer suppression and promotion. Science 2011; 331(6024):1565–70. https://doi.org/10.1126/science.1203486.

[2] Hanahan D, Weinberg RA. The hallmarks of cancer: the next generation. Cell 2011;144:464–74. https://doi.org/10.1016/j.cell.2011.02.013.

[3] Yao H, Wang H, Li C, Fang JY, Xu J. Cancer cell-intrinsic PD-1 and implications in combinatorial immunotherapy. Front Immunol 2018;9:1774. https://doi.org/10.3389/fimmu.2018.01774.

[4] Ratner L, Waldmann TA, Janakiram M, Brammer JE. Rapid progression of Adult T-cell leukemia-lymphoma after PD-1 inhibitor therapy. N Engl J Med 2018;378(20):1947–8. https://doi.org/10.1056/NEJMc1803181.

[5] Jiang P, Gu S, Pan D, Fu J, Sahu A, Hu X, et al. Signatures of T cell dysfunction and exclusion predict cancer immunotherapy response. Nat Med 2018;24(10):1550–8. https://doi.org/10.1038/s41591-018-0136-1.

[6] Auslander N, Zhang G, Lee JS, Frederick DT, Miao B, Moll T, et al. Robust prediction of response to immune checkpoint blockade therapy in metastatic melanoma. Nat Med 2018;24(10): 1545–9. https://doi.org/10.1038/s41591-018-0157-9.

[7] Galluzzi L, Buqué A, Kepp O, Zitvogel L, Kroemer G. Immunological effects of conventional chemotherapy and targeted anticancer agents. Cancer Cell 2015;28:690–714. https://doi.org/10.1016/j.ccell.2015.10.012.

[8] Brown JS, Sundar R, Lopez J. Combining DNA damaging therapeutics with immunotherapy: more haste, less speed. BJC 2017:1–13. https://doi.org/10.1038/bjc.2017.376.

[9] Yan Y, Kumar AB, Finnes H, Markovic SN, Park S, Dronca RS, et al. Combining immune checkpoint inhibitors with conventional cancer therapy. Front Immunol 2018;9:1739. https://doi.org/10.3389/fimmu.2018.01739.

[10] Jiang W, Chan CK, Weissman IL, Kim BYS, Hahn SM. Immune priming of the tumour microenvironment by radiation. Trends Cancer 2016;2:638–45. https://doi.org/10.1016/j.trecan.2016.09.007.

[11] Napoletano C, Bellati F, Landi R, Pauselli S, Marchetti C, Visconti V, et al. Ovarian cancer cytoreduction induces changes in T cell population subsets reducing immunosuppression. J Cell Mol Med 2010;14(12):2748–59. https://doi.org/10.1111/j.1582-4934.2009.00911.x.

[12] Reck M, Bondarenko I, Luft A, Serwatowski P, Barlesi F, Chacko R, et al. Ipilimumab in combination with paclitaxel and carboplatin as first-line therapy in extensive disease-small-cell lungcancer: results from a randomized, double-blind, multicenter phase 2 trial. Ann Oncol 2013;24:75–83. https://doi.org/10.1093/annonc/mds213.

[13] Park SE, Lee SH, Ahn JS, Ahn MJ, Park K, Sun JM. Increased response rates to salvage chemotherapy administered after PD-1/PD-L1 inhibitors in patients with non-small cell lung cancer. J Thorac Oncol 2018;13(1):106–11. https://doi.org/10.1016/j.jtho.2017.10.011.

[14] https://www.merckgroup.com/content/dam/web/corporate/non-images/press-releases/2018/dec/en/JAVELIN-Ovarian-100-Press-Release-EN.pdf.

[15] https://www.merckgroup.com/content/dam/web/corporate/non-images/press-releases/2018/nov/en/JAVELIN-Ovarian-200-Press-Release-EN.pdf.

[16] Alberts DS, Marth C, Alvarez RD, Johnson G, Bidzinski M, Kardatzke DR, et al. Randomized phase 3 trial of interferon gamma-1b plus standard carboplatin/paclitaxel versus carboplatin/paclitaxel alone for first-line treatment of advanced ovarian and primary peritoneal carcinomas: results from a prospective designed analysis of progression-free survival. Gynecol Oncol 2008;109:174–81. https://doi.org/10.1016/j.ygyno.2008.01.005.

[17] Baert T, Verschuere T, Van Hoylandt A, Gijsbers R, Vergote I, Coosemans A. The dark side of ID8-Luc2: pitfalls for luciferase tagged murine models for ovarian cancer. J Immunother Cancer 2015;3:57. https://doi.org/10.1186/s40425-015-0102-0.

[18] Wahba J, Natoli M, Whilding LM, Parente-Pereira AC, Jung Y, Zona S, et al. Chemotherapy-induced apoptosis, autophagy and cell cycle arrest are key drivers of synergy in chemo-immunotherapy of epithelial ovarian cancer. Cancer Immunol Immunother 2018;67(11):1753–65. https://doi.org/10.1007/s00262-018-2199-8.

[19] Peng J, Hamanishi J, Matsumura N, Abiko K, Murat K, Baba T, et al. Chemotherapy induces programmed cell death-ligand 1 overexpression via the nuclear factor-κB to Foster an immunosuppressive tumour microenvironment in ovarian cancer. Cancer Res 2015;75(23):5034–45. https://doi.org/10.1158/0008-5472.

[20] Yan Y, Cao S, Liu X, Harrington SM, Bindeman WE, Adjei AA, et al. CX3CR1 identifies PD-1 therapy-responsive CD8+ T cells that withstand chemotherapy during cancer chemo-immunotherapy. JCI Insight 2018;3(8). https://doi.org/10.1172/jci.insight.97828. pii: 97828.