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PERSPECTIVE ARTICLE

Immunogenic cell death: Chemoimmunotherapy in the clinic

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ABSTRACT

Although cancer chemotherapy has historically been considered immune suppressive, we now understand that combining chemoimmunotherapy incites a mechanism called Immunogenic cell death. These mechanisms are now moving from concepts to the clinic. Recently dramatic advances in lung cancer treatment by combining chemotherapy with immunotherapy have led the way to this new frontier in cancer medicine. We will explain the mechanism behind ICD and how it will perhaps breathe a new life into chemotherapy use in cancer, not front and center but as a helpful hand to immunotherapy.

Keywords: immunogenic cell death (ICD); chemoimmunotherapy

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Abbreviations:

check point inhibitors (CPI); ICD= Immunogenic cell death; CDAMs= cell death-associated molecules; Mo. = months; NA = not available; OS = overall survival; PFS = progression-free survival; ORR = overall response rate; HR = Hazard Ratio; RA = Rheumatoid arthiritis

Background

We now believe that how cells die during chemotherapy is critical[1]; although cancer chemotherapy has historically been considered immune suppressive and has been assumed to be detrimental to any potential immune response[2]. Certain chemotherapies can augment tumor immunity by “Immunogenic cell death” (ICD), and apoptosis is not A non-immunogenic event as it has been thought to be[1,3]. Inciting ICD is dependent on the drug its dose, and the schedule of chemotherapy administration[4,5]. However, certain types of apoptotic cell death can lead to activation of the adaptive arm of the immune system and disrupt strategies that tumors use for evasion of immune surveillance[1,5].

Non-immunogenic vs Immunogenic Cell death

Non-immunogenic cell death involves cell membrane breakdown and release of phosphatidylserine (PS) which are non-immunogenic parts of a cell membrane which gets engulfed by macrophages leading to sequestration of any tumor antigens from immune surveillance[6]. PS down plays this process further by upregulating TGF β (Transforming growth factor-β) and Interleukin-10 thereby making the death of the tumor cell a non-immunogenic event thereby bypassing the adaptive

arm of the immune system[7].

Some instances of cell apoptosis induced by chemotherapy and or radiation appear to be more efficient at eliciting the adaptive immune system rather than tumor cell undergoing necrosis or osmotic lysis, suggesting that clearance of apoptotic and necrotic cells in vivo is rather different[8,9].

The ability of cancer cells to elicit an immune response is perhaps dictated by CDAMs (cell death-associated molecules) emitted a dying tumor cell[1,8-10]. CDAMs that are exposed on the surface of tumor cells or released include calreticulin (CRT), ATP, high mobility group box 1 (HMGB1) etc. These help in exerting a potent immunostimulatory effect[9].

Conventional chemotherapeutics although may be immunosuppressive may also potentiate for enhanced immunotherapeutic outcome during the immune reconstitution phase following chemotherapy induced lymphopenia[9,11]. One mechanism is through stimulation of MHC class I expression and expressing tumor antigen expression referred to as “epitope spreading”. The altered MHC class I peptides expression, expression of altered normal proteins, defective ribosomal products (DRiPs) peptides generated by prematurely terminated and misfolded peptides etc. tags the cancer cells to be recognized by T cells for cell death[9,12].

There also seems to be distinct antineoplastic agents at narrow dosing range that improve the immunogenicity of tumors as they stimulate them to emit various immunostimulatory signals called DAMP (Damage associated molecular signals)[1,13]. Typically, **ER Stress** response in tumor cells leads to CRT exposure which signals to dendritic cells to engulf the tumor[9]. **Premortem autophagy** leads to ATP secretion and extracellular ATP acts on so-called purinergic receptors including metabotropic P2RY2 and ionotropic P2RX7 receptors cajoling DC precursors and neutrophils into the tumor bed expressing CD11c(+)CD11b(+)Ly6C(hi) engulfing tumor antigens in situ and presented them to T lymphocytes in an anthracycline exposed murine models[14]. **Secondary necrosis** leads to HMGB1[15], annexin A1 (ANXA1) release binding to TLR4 (Toll-like receptors) on mature dendritic cells that process the antigen this can be subverted by TLR4 SNP or HMGB1 loss[1,16]. DNA damaging agents has been shown to stimulate the expression of death receptors. FAS (also known as CD95) and TNF-related apoptosis-inducing ligand (TRAIL) receptors 1,2 on tumor cell surface[17] and in the presence of their respective ligands (FASL)/TRAIL, produced by immune effector cells[18] can induce immunogenic cell death[19].

Through multiple cytokines and chemokines, including CXCL1, CCL2, IL-6, and IL-8 these tumors become susceptible to the cytotoxic activity of several innate and adaptive immune effectors like NK cells[20] further increasing CRT exposure[21].

We are now able to somewhat understand as to how to activate Antigen-presenting cells, and T cells in patients with advanced disease, whose immune systems have weakened[22]. Intact immunogenicity is required in, a large part, to effectively prime antitumor CD8+ T cells[23]. In this respect, the process of tumor cell death will determine whether the initial interaction between the DC and the tumor cell yields an event of immunologic significance or not[4].

Necrosis induced by therapy is a source of antigenic substrate for Dendritic cells to present to T cells[4,9,22]. Obeid et al. suggested that some chemotherapy agents can induce more immunogenic cell death than others[22].

Many anticancer agents used at their maximum tolerated dose can exert myelosuppressive and immunosuppressive effects[24]. Anticancer agents used at clinically useful doses (usually below the maximum tolerated dose) may mediate rapid immunostimulatory effects[9].

For instance, the vaccination of cancer patients receiving standard-of-care chemotherapy can result in vigorous immune responses challenging the notion that chemotherapeutics only causes immunosuppression[9]. Ipilimumab can effectively be combined with antineoplastic agents such as fotemustine and temozolomide (for the treatment of metastatic melanoma) or paclitaxel plus carboplatin (in individuals bearing non-small-cell lung carci-

noma)[25,26]. Combination treatments of chemoimmunotherapy would not have been effective if chemotherapy only led to severe immunosuppression[9,13,22].

Recent Clinical Data

Despite the excitement surrounding checkpoint inhibitors, most patients do not respond to immunotherapy. There is biological sense in combining chemotherapy with immunotherapy to enhance their efficacy[27].

We have made incredible progress in bringing the concept of ICD from a concept to clinic. The recent AACR and ASCO presentation of chemo-immunotherapy trials and their success have led the way to possible change of the standard of care **(Table 1)**.

Tables 1. Nivolumab

NCT Number	Title	Recruitment	Phases	Start Date	Completion Date
NCT02434081	NIvolumab Consolidation With Standard First-line Chemotherapy and Radiotherapy in Locally Advanced Stage IIIA/B Non-Small Cell Lung Carcinoma (NICOLAS)	Active, not recruiting	Phase 2	Aug-15	Aug-19
NCT02659059	Nivolumab in Combination With Ipilimumab (Part 1); Nivolumab Plus Ipilimumab in Combination With Chemotherapy vs. Chemotherapy Alone (Part 2) as First Line Therapy in Stage IV Non-Small Cell Lung Cancer (CheckMate 568)	Recruiting	Phase 2	Feb-16	24-Jan-22
NCT02477826	An Investigational Immuno-therapy Trial of Nivolumab, or Nivolumab Plus Ipilimumab, or Nivolumab Plus Platinum-doublet Chemotherapy, Compared to Platinum Doublet Chemotherapy in Patients With Stage IV Non-Small Cell Lung Cancer (NSCLC)-(CheckMate 227)	Recruiting	Phase 3	Aug-15	Dec-20
NCT03215706	A Study of Nivolumab and Ipilimumab Combined With Chemotherapy Compared to Chemotherapy by Itself as the First Treatment Given for Stage IV Non-Small Cell Lung Cancer (NSCLC) (CheckMate 9LA)	Recruiting	Phase 3	Jul-17	25-May-20
NCT02864251	A Study of Nivolumab + Chemotherapy or Nivolumab + Ipilimumab Versus Chemotherapy in Patients With EGFR Mutation, T790M Negative NSCLC Who Have Failed 1L EGFR TKI Therapy (CheckMate 722)	Recruiting	Phase 3	Oct-16	31-Dec-23
NCT01454102	Study of Nivolumab (BMS-936558) in Combination With Gemcitabine/Cisplatin,	Active, not recruiting	Phase 1	Dec-11	30-Nov-17

	Pemetrexed/Cisplatin, Carboplatin/Paclitaxel, Bevacizumab Maintenance, Erlotinib, Ipilimumab or as Monotherapy in Subjects With Stage IIIB/IV Non-small Cell Lung Cancer (NSCLC) (CheckMate 012)				
NCT03168464	Radiation and Immune Checkpoints Blockade in Metastatic NSCLC (BMS # CA209-632)	Not yet recruiting	Phase 1/2	Sep-17	30-Dec-22
NCT02967133	A Study of Nivolumab +/- Nab-paclitaxel in Non-small Cell Lung Cancer	Not yet recruiting	Phase 2	Dec-16	Dec-20
NCT02309177	Safety Study of Nivolumab With Nab-Paclitaxel Plus or Minus Gemcitabine in Pancreatic Cancer, Nab-Paclitaxel/Carboplatin in Stage IIIB/IV Non-Small Cell Lung Cancer or Nab-Paclitaxel in Recurrent Metastatic Breast Cancer	Recruiting	Phase 1	14-Jan-15	26-Oct-18
NCT02423954	Study of Nivolumab Plus Chemotherapy (NivoPlus)	Active, not recruiting	Phase 1|Phase 2	Apr-15	Apr-18
NCT03085914	A Study of Epacadostat in Combination With a PD-1 Inhibitor and Chemotherapy in Subjects With Advanced or Metastatic Solid Tumors (ECHO-207)	Recruiting	Phase 1|Phase 2	02-May-17	Oct-22

Tables 1. PEMBROLIZUMAB

NCT Number	Title	Recruitment	Phases	Start Date	Completion Date
NCT02775435	A Study of Carboplatin-Paclitaxel/Nab-Paclitaxel Chemotherapy With or Without Pembrolizumab (MK-3475) in Adults With First Line Metastatic Squamous Non-small Cell Lung Cancer (MK-3475-407/KEYNOTE-407)	Recruiting	Phase 3	Jun-16	Aug-19
NCT02591615	Optimal Sequencing of Pembrolizumab (MK-3475) and Standard Platinum-based Chemotherapy in First-Line NSCLC	Recruiting	Phase 2	Mar-16	Dec-19
NCT02564380	Study of Pembrolizumab Maintenance Following First-Line Platinum Based Chemotherapy in Patients With Metastatic Squamous - Non-Small Cell Lung Cancer (sNSCLC)	Recruiting	Phase 2	Mar-16	Sep-19
NCT03242915	Pembrolizumab in Combination With Platinum-based Doublet Chemotherapy in Patients With EGFR Mutation and ALK Positive NSCLC (Non-Small Cell Lung Cancer) With Progressive Disease Following Prior Tyrosine Kinase	Not yet recruiting	Phase 2	Aug-17	Aug-22

	Inhibitors (TKIs)				
NCT02578680	Study of Platinum + Pemetrexed Chemotherapy with or Without Pembrolizumab (MK-3475) in Participants With First Line Metastatic Non-squamous Non-small Cell Lung Cancer (MK-3475-189/KEYNOTE-189)	Active, not recruiting	Phase 3	Jan-16	26-Apr-19
NCT02039674	A Study of Pembrolizumab (MK-3475) in Combination with Chemotherapy or Immunotherapy in Participants With Lung Cancer (MK-3475-/KEYNOTE-021)	Active, not recruiting	Phase 1|Phase 2	Feb-14	Oct-19
NCT02621398	Pembrolizumab, Paclitaxel, Carboplatin, and Radiation Therapy in Treating Patients With Stage II-IIIB Non-Small Cell Lung Cancer	Recruiting	Phase 1	Apr-16	Sep-19
NCT01840579	Study of Pembrolizumab (MK-3475) Monotherapy in Advanced Solid Tumors and Pembrolizumab Combination Therapy in Advanced Non-small Cell Lung Cancer/ Extensive-disease Small Cell Lung Cancer (MK-3475-011/KEYNOTE-011)	Recruiting	Phase 1	Apr-13	15-Dec-19
NCT03134456	Pembrolizumab for Metastatic NSCLC Patients Expressing PD-L1 Who Have Their Own PDX	Not yet recruiting	Phase 4	Aug-17	29-Feb-20
NCT02987998	Neoadjuvant Chemoradiation Plus Pembrolizumab Followed by Consolidation Pembrolizumab in NSCLC	Recruiting	Phase 1	May-17	Jan-20

Among the initial clinical data was the cohort C of KEYNOTE-021, the dose-finding cohort for the combination of pembrolizumab plus carboplatin and pemetrexed, there was no apparent relationship between PD-L1 expression and response, with more than 60% of patients achieving a response across the PD-L1 tumor proportion score subgroups with PFS >10 months[28].

KEYNOTE-021 showed the addition of pembrolizumab to standard-of-care chemotherapy followed by pembrolizumab for 2 years and pemetrexed maintenance therapy significantly improved objective response (55%) compared with chemotherapy alone in chemotherapy naïve patients with NSCLC[29]. This combination significantly prolonged progression-free survival (PFS) in this non-squamous NSCLC population to 13·0 months for pembrolizumab plus chemotherapy compared to 8·9 months for chemotherapy alone.

This concept is being studied in the KEYNOTE-189 study and the KEYNOTE-407 study of carboplatin and paclitaxel or nab-paclitaxel with or without pembrolizumab for squamous histology (ClinicalTrials.gov, number NCT02775435)[29]. In May 2017 FDA approved pembrolizumab and platinum doublet-based chemotherapy as first-line treatment in metastatic non-squamous NSCLC based on cohort G of the phase II KEYNOTE-021 study.

Keynote 189 was the natural phase III extension of the earlier studies in first-line metastatic non-squamous NSCLC patients. Patients were randomized in a 2:1 fashion, to receive platinum and pemetrexed-based chemotherapy with either pembrolizumab (test arm) or placebo (control arm).

After a 10.5-month median follow-up; median OS was not reached in the pembrolizumab arm, versus 11.3 months in the control arm. The

pembrolizumab test arm was 51 percent less likely to die, compared with 58% reduction in the high PD-L1 group. However, a clear survival benefit was seen across all groups despite a 50 percent crossover rate[30].

Similarly, the IMpower150 trial met its co-primary PFS and OS endpoints, across all PD-L1 subgroups in first-line treatment of non-squamous NSCLC with the combination of atezolizumab and bevacizumab plus a platinum doublet. The median OS with the presence of atezolizumab was 19.2 months compared with 14.7 months in the non-PD-L1 inhibitor group of Bevacizumab, carboplatin and platinum (HR, 0.78)[31].

The ImPOWER 131, a phase III study of squamous NSCLC recently presented at ASCO 2018 showed a doubling of PFS. Twenty nine percent of all patients, regardless of PD-L1 expression, had a reduced risk of death compared with those who received chemotherapy alone[32]. The Checkmate 227 is looking at activity in combination of immunotherapies. Recently published data showed a significant longer progression-free survival with first-line nivolumab plus ipilimumab than with chemotherapy among patients with NSCLC and a high tumor mutational burden, irrespective of PD-L1 expression level. Median PFS was 7.2 months in the nivolumab/ipilimumab arm vs 5.5 months in the chemotherapy arm (HR = 0.58)[33].

Conclusion

Recent exciting changes in front lie treatment of lung cancer combining chemotherapy and immunotherapy have brought the concept of immunogenic cell death to the clinic and promises to usher a new realm in the treatment of metastatic lung cancer. The role of chemotherapy may not be front and center but is not over as of yet.

Conflict of Interest

The author declared no conflict of interest.

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