Review Article

A narrative review of synergistic drug administration in unresectable locally advanced non-small cell lung cancer: current landscape and future prospects in the era of immunotherapy

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Abstract: Based on the PACIFIC study, the standard care of unresectable locally advanced non-small cell lung cancer (LA-NSCLC) shifted from concurrent chemo-radiotherapy (CCRT) alone to CCRT followed by durvalumab consolidation in 2017. In the era of immunotherapy, two kinds of therapeutic drugs are involved in the management of LA-NSCLC: chemotherapeutics and anti-PD-1/PD-L1 agents. However, the best choices of systematic chemotherapy, immunotherapy, and treatment schedule remain controversial. The immune modulation effects of chemotherapy, as well as the potential immunosuppressive impact of pretreatment medications, should be taken into consideration. Indeed, chemotherapeutics are double-edged swords to immunotherapy, with both stimulatory and suppressive effects on the immune system. Moreover, low-dose chemotherapy is reported to enhance anti-tumor immune responses with reduced toxicities. As for glucocorticoids, there is no consensus about its exact impact on the efficacy of immunotherapy. In addition, the timing of anti-PD-1/PD-L1 agent related to CCRT has three modes: induction, concurrent, and consolidation therapy. Although CCRT followed by durvalumab consolidation is the standard of care, the best sequence of immunotherapy and chemo-radiotherapy is still under debate. Furthermore, the efficacy and toxicity of various PD-1/PD-L1 inhibitors should be compared, especially in the background of CCRT. In this review, we will summarize the detailed knowledge about chemotherapeutics and anti-PD-1/PD-L1 axis agents, and discuss the potential implications in designing novel, effective treatment strategies for LA-NSCLC.

Keywords: Immunotherapy; lung cancer; chemotherapy; stage III; locally advanced

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Introduction

The paradigm of treatment for unresectable locally advanced non-small cell lung cancer (LA-NSCLC) experienced the shift from radiotherapy alone to combined chemotherapy and radiotherapy (CRT) over two decades ago. In 1980s, based on the result of RTOG7301, radical radiotherapy (RT) alone was the standard care of LA-NSCLC, with a 2-year survival of 25% and 5-year survival of only 5% (1,2). In 1995, a high-quality meta-analysis provided evidence that radical radiotherapy plus chemotherapy resulted in absolute benefits of 3% and 2% at 2- and 5-year survival compared with radiation alone (3).

Thereafter, cisplatin-based chemotherapy plus radiotherapy became the new standard of care for LA-NSCLC. Among the two modes of combined CRT: concurrent CRT (CCRT) and sequential CRT (SCRT), several randomized trials and a meta-analysis based on the individual patients data showed that CCRT could increase the overall survival (OS) and progression-free survival (PFS) for patients with LA-NSCLC patients over SCRT, although at the expense of increased manageable acute esophageal toxicity (4). Moreover, several phase III randomized trials demonstrated induction (5) and consolidation (6,7) chemotherapy beyond CCRT had no further benefit. Thus, CCRT alone became the standard of care for LA-NSCLC before immunotherapy involved.

In the next two decades, many attempts have been made to improve the efficacy and/or the tolerance of CCRT in LA-NSCLC, all of which failed to introduce considerable advancement (7,8). Recently, multiple randomized trials demonstrated that inhibitors of the programmed cell death-1 (PD-1) pathway could provide significant clinical benefits for patients with metastatic NSCLC and several early phase clinical trials incorporating anti-programmed cell death-ligand 1(PD-L1) or anti-PD-1 agents showed encouraging antitumor activity for patients with LA-NSCLC (9,10). In the HRCN LUN14-179 study, consolidation with anti-PD-1 agent Pembrolizumab after CCRT was found to be well tolerated (11). In the DETERRED study, consolidation using anti-PD-L1 agent Atezolizumab in combination with two cycles of carboplatin plus paclitaxel after CRT showed preliminary efficacy (12). Finally, the landscape for the management of unresectable LA-NSCLC changed in 2017. Based on the result of the PACIFIC study (13), immunotherapy has opened up a new era in the treatment for LA-NSCLC. The PACIFIC study has corroborated the benefits brought by consolidation anti-PD-L1 agent durvalumab compared to placebo after CCRT (13,14). For PFS, the HR was 0.51 in favor of the durvalumab group, with 1-, 2-year, and median PFS results of 55.7%, 49.5%, and 17.2 months. For OS, the HR was 0.68, also favoring the immunotherapy arm. One-, two-year, and median OS results were 83.1%, 66.3%, and not reached, respectively (P=0.003). The standard of care for LA-NSCLC has then been updated to the PACIFIC treatment pattern by now.

So currently, systematic therapy is vital in the management of LA-NSCLC, with now two kinds of therapeutic drugs involving in the standard treatment: chemotherapeutics and anti-PD-1/PD-L1 axis agents. The new treatment mode also raises important questions, such as the future directions of systematic therapy for LA-NSCLC in the era of immunotherapy. In this review, we will summarize the current status regarding the optimal choice of systematic drugs, with a particular focus on prospects and challenges in the era of cancer immunotherapy for LA-NSCLC (*Figure 1*). Information used to write this review was collected from PUBMED and EMBASE databases (date of the last search 10 January 2020). The key words used for searching are chemotherapy, radiotherapy for LA-NSCLC and their combination with immunotherapy. In addition, several reference lists of identified articles were searched manually.

We present the following article in accordance with the Narrative Review Checklist (available at http://dx.doi.org/10.21037/tlcr-20-512).

Chemotherapy: the optimal regimen

There have been multiple prospective randomized controlled clinical trials (4) comparing the efficacy of different chemotherapy regimens used in CCRT, with most of them failing to show whichever was better, except for one study (15). This study is a multicenter randomized phase III study performed in China (15), a total of 200 LA-NSCLC patients were treated with 60–66 Gy of thoracic radiation therapy concurrent with either etoposide and cisplatin (EP arm), or paclitaxel and carboplatin weekly protocol (PC arm). They found EP arm was superior to the PC arm in terms of OS, with 3-year OS significantly higher in EP arm (P=0.024). However, this result was inconsistent with the analysis based on the big real-world data from Veteran Health Administration of the United States, which showed LA-NSCLC patients treated with EP versus PC had similar OS, but EP was associated with increased morbidity (16). Thus, the superiority of EP versus PC is still controversial. At present, several platinum-based chemotherapy protocols can be chosen in the clinical settings for LA-NSCLC during CCRT, according to the guidelines (17,18), except the agent associated with increased radiation toxicities, such as gemcitabine to pulmonary toxicity.

When the immunotherapy involved, several concerns should be taken into consideration because chemotherapeutics and even their pretreatment medications such as glucocorticoids (GCs) may have an impact on the immune system and thus affect the therapeutic response of immunotherapy.

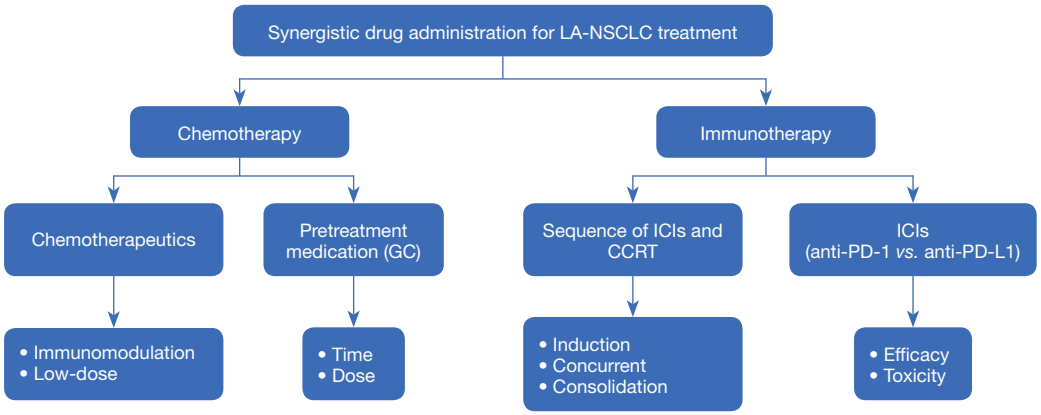

Figure 1 Consideration of the optimal choice of systematic drugs for unresectable locally advanced non-small cell lung cancer (LA-NSCLC). GC, glucocorticoid; ICIs, Immune checkpoint inhibitors; CCRT, concurrent chemo-radiotherapy; PD-1, programmed cell death-1; PD-L1, programmed cell death ligand 1.

Chemotherapeutics as immune modulators

Chemotherapy has long been recognized as an immunosuppressive intervention, due to the cytotoxic effects of chemotherapeutics to the immune cells as well as lymphoid tissues. The immunosuppressive side effects of chemotherapeutics mainly manifest as bone marrow suppression, including myelo- and lymphopenia (19), resulting from impaired T lymphocytes, B lymphocytes, and NK cells. For instance, in the preclinical researches, etoposide and camptothecin were shown to induce a rapid production of ceramide, which can initiate the apoptotic cascade signaling in peripheral T lymphocytes (20); paclitaxel could down-regulated the intracellular pathways involving JNK/p38 MAP kinases, thus producing a selective inhibition of LPS-induced B-cell proliferation in mouse model (21); and taxol treatment inhibited NK cell cytotoxicity by altering microtubule assembly (22). Chemotherapeutics induced immunosuppressive effects are also commonly seen in the clinical settings, for example, the populations of B cells, $CD4^+$ and $CD8^+$ T cells were shown to be significantly decreased by high-dose sequential chemotherapy and did not recover even long after the first cycle of therapy (23).

However, accumulative evidence emerged recently that chemotherapeutics also have the immunomodulation effects on tumor microenvironment, with some of them being positive to the antitumor immune response (24). For instance, among the commonly used chemotherapeutics in NSCLC, cisplatin has been found to have antitumor immune-stimulatory effect by upregulating MHC class I expression on cancer cells, promoting recruitment and proliferation of immune effector cells, and downregulating the immunosuppressive molecules (25); carboplatin could mediate the activation of murine macrophage and then enhance IL-1α and TNF-α activities (26); gemcitabine and docetaxel were found to reduce the inhibitory immune cells, such as MDSCs (27,28); and paclitaxel was able to increase immune stimulatory factors by promoting the tumoricidal activity of M1 macrophage as well as inducing apoptosis of immunosuppressive cells, such as Tregs (29-31). Tumor response to conventional chemotherapy has been indicated to be partly attributed to the increased immunogenicity of malignant cells and inhibited immunosuppressive circuitries, which are promoted by chemotherapeutic (32). On the other side, tumor microenvironment immunomodulation by chemotherapeutics also would be negative. A notable example is that some chemotherapeutic agents can induce PD-L1 expression on tumor cells (33), which is a process of immune escape of tumor and associated with poor outcomes in several cohorts of patients with cancer (32,34). A more comprehensive description of the immunomodulation effects of chemotherapeutics goes beyond the scope of our review and can be found elsewhere (24).

The immunomodulation effects of chemotherapeutics form the basis of combination treatment with chemotherapy and immunotherapy. The clear example comes from the success of combing anti-PD-1/PD-L1 with chemotherapeutic agents in NSCLC (35-38), to which tumor PD-L1 expression increased by chemotherapy should at least partly contribute. However, chemotherapy is a double-edged sword to immunotherapy, as described above.

There exist clear variations in the immune stimulatory effects of different chemotherapeutics. So, the detailed knowledge of these differences may have a profound impact on the design of novel, effective treatment options, especially in chemotherapy agent choice for LA-NSCLC, when immunotherapy involved.

The other issue in chemotherapy lies in the administration schedule, among which the dosage of chemotherapeutics is of most importance. For more than half a century, to kill as many tumor cells as possible, chemotherapeutics are often administered in single doses, or short courses of therapy at the maximum tolerated dose (MTD) (39). Indeed, for some chemo-sensitive malignancies, such as acute lymphoblastic leukemia and Hodgkin's lymphoma, MTD chemotherapy may lead to complete remission or even cure. However, significant advances of MTD seem to have reached a plateau for solitary tumors over the past two decades, due to drug resistance and highly toxic (40). In the meantime, the low-dose protocols such as metronomic chemotherapy attracted growing scientific and clinical interest (41), originating from the potential to overcome drug resistance by shifting the therapeutic target from tumor cells to tumor vasculature (42). Low-dose chemotherapy also holds merit in reducing specific toxicities (43). In unresectable LA-NSCLC, low-dose chemotherapy has also been tested in combination with radiotherapy as the radio-sensitizer, but with conflicting results (44).

However, in the era of immunotherapy, we need reconsideration of low-dose chemotherapy, because the effects of chemotherapeutics on immune system depend significantly on their dosage. For instance, in mouse models, cisplatin and paclitaxel administrated with MTD would induce the toxicity to all immune cells and thus cause significant myelosuppression, while the lower dose protocol could reduce immunosuppression of tumor microenvironment, and even elicit tumor-specific antitumor $CD8^+$ T-cell responses (45); in the clinical setting, oral administration of high dosage cyclophosphamide (200 mg/day) was found to induce a profound decrease in the circulating lymphocyte number, NK cell-dependent cytotoxicity, and T cell proliferation capacity, while a lower dosage (100 mg/day) selectively depleted circulating immunosuppressive cell Tregs, and restored T cell and NK effector functions (46). The detailed mechanisms regarding the impact of low-dose chemotherapy on the immune system have been described elsewhere (47).

Low-dose chemotherapy has also been explored in combination with anti-PD-1/PD-L1 agent. A preclinical study showed combining low-dose gemcitabine, a CDK1 inhibitor, and PD-L1 antibody significantly increased anti-tumorigenic $CD8^+$ cytotoxic T-cell, DC and M1 macrophage populations, and simultaneously decreased the populations of immunosuppressive M2 macrophage and MDSC in SCLC (48). An interim analysis of clinical study demonstrated that weekly low-dose carboplatin (AUC =1) and paclitaxel (25 mg/m^2) combined with pembrolizumab was well tolerated in advanced NSCLC patients with poor performance status, and of noted,70% of the patients received combined therapy achieved PR, comparing to only 20% in the single pembrolizumab treatment group; the combination group experienced a significant decrease in absolute numbers of immunosuppressive MDSC subpopulation and an increase in activated $CD4^+$ T cells in the blood (49).

There has been no report of low-dose chemotherapy in LA-NSCLC when immunotherapy involved. However, this field needs to be investigated in the era of immunotherapy due to the mechanisms described above, and additionally, the unique advantage of radio-sensitive effects of several chemotherapeutics was illustrated in their low-dose levels (50,51).

Pretreatment medication

GCs are commonly used to control the symptoms and alleviate the side effects of treatment modalities in cancer treatment. They are also administrated as preconditioning for some chemotherapy agents such as pemetrexed, paclitaxel, and docetaxel, which are often used in NSCLC. The reason for choosing GCs as the pretreatment medication is attributed to the well-known anti-inflammatory and immunosuppressive effects of GCs.

GCs modulate immune function through the glucocorticoid receptor (GR), which belongs to the nuclear receptor superfamily of ligand-activated transcription factors. Upon binding of GCs, GR translocated to the nucleus where it binds to DNA sequences and regulates the transcription of various kinds of immune-related genes, such as cytokines, chemokines, interferons, as well as other immune-modulating molecules, with the help of a large number of co-activators and co-repressors (52,53). At the cellular level, GCs suppress the immune response by modulating the differentiation, activation, and function of both lymphocytes and myeloid cells, especially T cells (54). GCs mediate their immunosuppression effect on T cells through both genomic actions by regulating the transcription of viral genes (such as GILZ, GITR) and non-

genomic actions by the interaction between GR and the T-cell receptor complex (55,56). The immunosuppression effects of GCs are well recognized in their treatment for autoimmune diseases.

It is still an open question of whether GCs administration could significantly affect the efficacy of immune checkpoint inhibitors. In the Keynote-407 study, treatment efficacy was similar among the untreated metastatic squamous NSCLC patients who received paclitaxel, which needed preconditioning with GCs, and those who received GC-free nab-paclitaxel (36). Also, the response rate (RR) was similar in advanced melanoma patients who did receive system GCs or other suppressive immune-modulating agents and patients who did not (57). Furthermore, in a study of metastatic melanoma patients treated by CTLA-4 blockade, high-dose of system steroid administration in patients with high-grade immune-related adverse events (IRAE) had no significant effect on the duration of response (P=0.23) (58). However, Arbour *et al*. reported baseline GC use of ≥10 mg of prednisone equivalent to indicate poorer PFS (HR: 1.3) and OS (HR: 1.7) in NSCLC patients who treated with PD-1/PD-L1 inhibitors, and they recommended prudent use of GCs at the time of initiating immune checkpoint inhibitors (59).

Nevertheless, another study found that the differences in treatment efficacies between patients receiving a higher dose of baseline GCs and those who did not mainly depend on whether corticosteroids were administered for cancer-related palliative reasons or cancer-unrelated indications. Patients who received a higher dose of baseline GCs for palliative indications had significantly shorter survival, while no significant survival difference among patients receiving different levels of baseline GCs for cancer-unrelated indications (60). Until now, there is no consensus about the exact role of GCs on the efficacy of immunotherapy. Additionally, a recent study indicated that the administration of anti-TNF drugs for the treatment of steroid-refractory immune-related toxicity decreased patient's survival among 1,250 melanoma patients receiving immune checkpoint inhibitors (61). Future researches examining the exact effect of GCs as well as other immune-modulating drugs on the efficacy of immunotherapy, with prospective design and larger sample size, are called for.

As for the treatment of LA-NSCLC in the era of immunotherapy, chemotherapy without preconditioning may be favored, and the administration of low dose GCs for a limited duration of time in the case of side effect intervention and symptom control may be safe. However, high dose GCs or extended duration of usage should be in caution.

Immunotherapy

Immune checkpoint inhibitors (ICIs) are emerging as a frontline treatment for many cancers by blocking the immune escape mechanisms. Currently, the US Food and Drug Administration (FDA) has approved two classes of ICIs for clinical use: anti-PD-1/PD-L1 agents and anti-cytotoxic T-cell lymphocyte-associated protein 4 (CTLA-4) antibody. PD-1/PD-L1 or CTLA-4 served as brakes on immune system by blocking anti-tumor responses, while ICIs could reverse this effect. Based on the PACIFIC study, durvalumab (anti-PD-L1) treatment after CCRT is recommended for LA-NSCLC (13). Along with radiotherapy and chemotherapy, immunotherapy becomes a pillar of LA-NSCLC care.

A functional immune system is essential for successful ICIs therapy. Based on the density and location of tumor-infiltrating lymphocytes, the phenotypes of tumor immune microenvironment are classified into three categories: immune-desert, immune-excluded and immune-inflamed. The first phenotype features the absence of T cells and is associated with poor response to ICIs therapy. The immune-excluded tumors feature the presence of immune cells located in the periphery, which can not enter the center of tumor. The immune-inflamed tumors are characterized by abundant T cells in the center of tumor, and usually accompanied by the presence of PD-L1 expression, and thus respond well to ICIs. To obtain better response to ICIs, it is worthy to explore how to turn a tumor into "immune inflamed" (62).

Except for chemotherapy we discussed above, radiotherapy also has been found to have impacts on immune system. On one hand, radiotherapy could stimulate antitumor immune response through releasing tumor antigens and immune-activating cytokine (e.g., high-mobility group protein B1, interleukin 1β, interferon γ,tumor necrosis factor α) (63). On the other hand, radiotherapy may also have immune toxicity by inducing radiation-induced lymphopenia or activating immunosuppressive cytokines (e.g., transforming growth factor β) and cells (e.g., Tregs, M2 macrophage) (63,64).

Since the effects of chemotherapy and radiotherapy on the immune system are two-sided, the impacts of CRT on the anti-tumor immune response are complicated. In patients with head and neck cancer, adjuvant CRT contributed to the cultivation of immunosuppressive

microenvironment by increasing the number of Treg cells, elevating the secretion of TGF-β and decreasing the frequency of immune-active $CD4^+$ T cells (65). However, preoperative CRT was found to promote the anti-tumor immune response through decreasing the number and inhibiting the function of Tregs in pancreatic cancer (66). In addition, CRT was reported to enhance anti-tumor immunity by increasing the expression of various polyfunctional cytokines of $CD4^+$ T cells, leading to increased sensitivity to subsequent ICIs (67). As the immune status can be changed by CCRT, the response to anti-cancer therapy in LA-NSCLC may vary a lot according the sequence of immunotherapy and CCRT. The timing of immunotherapy related to CCRT in LA-NSCLC has three modes: induction, concurrent, and consolidation therapy.

Consolidation mode

At present, the standard of care supports the use of PD-L1 blockade durvalumab as consolidation treatment after CCRT for unresectable LA-NSCLC, which is derived from the success of PACIFIC trial (13,14). The timing of durvalumab involvement in the PACIFIC protocol design was initially based on the preclinical evidence suggesting that chemotherapy and radiotherapy may up-regulate PD-L1 expression on tumor cells (33,68,69), which is a predictive factor for a response to PD-1/PD-L1 antibodies. The phenomenon that CCRT could induce an elevator of cancer cell PD-L1 expression was also shown recently in the clinical setting in LA-NSCLC (70). The advantages of consolidation immunotherapy may also stem from that radiotherapy can alter the tumor microenvironment to promote more significant infiltration of immune effector cells (71-73), and the front CCRT can reduce the tumor burden, both of which will favor therapeutic response when immunotherapy participated. Also, the patients with progressive diseases, death, or with poor health after completion of CCRT will be picked out, so that those with good physical potential can be selected, and this group may be more suitable for immunotherapy. CCRT followed by durvalumab consolidation is the new standard care of LA-NSCLC, while CRT (either CCRT or SCRT) followed by other PD-1/PD-L1 inhibitors have also reported promising preliminary results (74-76).

Concurrent mode

Even with the PACIFIC trial, the best sequence of PD-1/PD-L1 blockades and CCRT in LA-NSCLC is still unclear. Of interest, the concurrent administration of a PD-1 inhibitor and radiation has been shown to increase immune activation over the sequential administration in mice models (69), suggesting there may be a room toward improving therapeutic effects through optimizing the timing of PD-1/PD-L1 blockade related to radiotherapy. Also, prior exploratory analysis from PACIFIC demonstrated that delivering durvalumab sooner after completion of CCRT (≤14 days) could potentially obtain more benefit (13). Thus, the field of combining concurrent PD-1/PD-L1 inhibitors and CCRT is of great clinical interest. However, there are several concerns about this mode in LA-NSCLC, with the first one about safety. Several preclinical types of research have shown that concurrent administration of anti-PD-1 antibody with thoracic irradiation will significantly increase pulmonary and cardio toxicities (77,78). And the toxicities enhanced by concomitant use of anti-PD-1/PD-L1 and chemotherapy compared to chemotherapy alone were also demonstrated in many large phase III trials in lung cancer (Keynote 189, Keynote 407, IMPOWER 130, 131, 132).

By now, two single-arm phases II trials (69,79) have been published to demonstrate the feasibility of combining concurrent anti-PD-1/PD-L1 antibody and definitive CCRT in LA-NSCLC according to the safeties. In the ETOP NICOLAS trial, LA-NSCLC patients received three cycles of platinum-based chemotherapy and concurrent radiotherapy (66 Gy/33 fractions), and the PD-1 antibody nivolumab started concurrently with radiotherapy. The interim safety analysis showed no unexpected AEs or increased toxicities were observed; among the 80 enrolled patients, 34% (19 grade 2 and 8 grade 3) experienced pneumonitis within 6 months (69). Although the pneumonitis was higher in NICOLAS than in the PACIFIC trial, it is comparable to the historical controls where patients treated with standard CCRT alone without immunotherapy have a 3–10% grade or higher rate of radiation pneumonitis (80). In the DETERRED study (79), the arm of concurrent treatment firstly applied CCRT with standard course radiotherapy (60–66 Gy/30–33 fractions) and weekly paclitaxel and carboplatin regimen and concurrent PD-L1 antibody atezolizumab to LA-NSCLC patients, the consolidation full dose paclitaxel and carboplatin with atezolizumab was then proceeded for 2 cycles for those with no evidence of disease progression, followed by maintenance atezolizumab for up to 1 year. The profile of general toxicity in the DETERRED trial was acceptable, with a 20% grade 3 or higher immune-

related AE rate. Thirteen percent grade 2 and 3% grade 3 pneumonitis occurred among the 30 patients treated with concurrent CCRT-immunotherapy; the rates are comparable to the PACIFIC trial. The status of combining concurrent CCRT-immunotherapy in LA-NSCLC is presently inconclusive base on the currently published studies, due to the small sample sizes and none of the randomized comparative groups. However, the preliminary results of these trials warrant further investigation, and several large related trials are being developed or underway, including PACIFIC 2 (NCT 03519971) and EA 5181 (NCT 04092283).

Induction mode

The other way to involve immunotherapy in LA-NSCLC is induction therapy, in which the immunotherapy agents are administrated before CCRT. Although more attention is now paid to the immunomodulation of the conventional treatment modalities such as chemotherapy and radiotherapy, several pieces of evidence also showed the impact of the immune system on the treatment effects of conventional therapies. For example, both macrophage abundance and T-cell abundance in tumors represent prognostic indicators for recurrence-free and OS in breast cancer treated with chemotherapy, with a poor T-cell infiltrate linking to a poorer prognosis (81); and in animal models, the efficacy of radiation is partly dependent on functional T-cell responses (82,83), and radiotherapy can be made more effective by improving T-cell immune responses (82-84). Thus, the local immune environment within a tumor may potentially affect the success or failure of chemotherapy and radiotherapy. Several studies have indicated that salvage chemotherapy after PD-1/PD-L1 blockades produced potentially improved efficacy in metastatic NSCLC (85,86). Also, several preclinical types of research revealed that the tumor response to PD-1/PD-L1 blockades mainly results from recruiting the effective periphery T-cell to invade tumors (87); and the multispectral analyses of the tumor with primary pathological response after neoadjuvant PD-1 blockade illustrated the new infiltration with PD-1-positive $CD8^+$ T cells in NSCLC (88), which suggest immunotherapy can remodel tumor local immune environment, with the potential of improving therapeutic effects of conventional treatments in some patients. All the above forms the theoretical basis of induction immunotherapy before CCRT. In the mice models, immunotherapy targeting another checkpoint, the anti-CTLA4 antibody was shown to be most effective when given before radiation, in part due to regulator T cell depletion (89). Other merits of induction immunotherapy lie in that the host systemic immune functions are not attacked by chemo and radiation therapy, which is suitable for the generation of antitumor immune responses, and that the possible tumor burden reduction by immunotherapy will favor the subsequence radiotherapy in respect of radiation toxicity.

There has been no report on the induction immunotherapy and CCRT in LA-NSCLC by now. The protocol of AFT-16 (NCT03102242) was announced in ASCO 2017, which is a single-arm phase II trial to explore the feasibility of induction atezolizumab followed by definitive CCRT in patients with LA-NSCLC, but the results have not yet been reported. The success or fail of induction mode depends on the effectiveness of immunotherapy because ineffective induction treatment will delay and thus be detrimental to the standard curative CCRT. However, the RR of the sole anti-PD-1/PD-L1 agents was relatively low in the non-selective population with NSCLC (90,91). PD-L1 expression on the tumor cell can predict the efficacy of anti-PD-1/PD-L1 alone in the first-line treatment for advanced NSCLC, with higher expression associated with better efficacy (92). So, there was a PD-L1 expression-driven trial designed in LA-NSCLC. In the ongoing SPRINT (NCT03523702) trial, the patients are stratified by the PD-L1 Tumor Proportion Score (TPS); the patients with TPS ≥50% will receive induction three cycles of pembrolizumab followed by radiation and sequential consolidation pembrolizumab, and otherwise will receive standard CCRT and consolidation therapy.

It should be noted that there are now several uncertainties in the PD-L1 test, including tumor heterogeneity, different potencies attributing to the different assays, variations in the criteria of pathologist judgment, etc. (93,94). Even when PD-L1 expression was higher than 50% (TPS ≥50%), the reported objective RRs were not high, such as 44.8% in Keynote 024 (95) and 39% in Keynote 042 (92), which indicate that potentially there are more than 50% patients will not benefit from induction PD-1 antibody even in this high-selected group. Combing immunotherapy and chemotherapy has been shown to improve treatment efficacy (35-38), but the impact of increased toxicities on the compliance of subsequent CCRT will be another issue. However, the idea of biomarker-driven immunotherapy is significant, which beckons for the more effective biomarkers. There should be a long way to the clinical practice of

induction mode in LA-NSCLC, with other issues also need be concerned, including pseudoprogression after immunotherapy which will make the delineation of radiation targets more complex, and immunotherapy induced hyper-progression which may let some patients lost the opportunity of cure by radical CCRT.

PD-1 versus PD-L1 antibodies

There are two types of anti-PD-1/PD-L1 axis agents: PD-1 inhibitors and PD-L1 inhibitors. Mechanically, the significant difference between the two types lies in that PD-1 inhibitors simultaneously block the binding between PD-1 and its ligands PD-L1 and PD-L2, while PD-L1 inhibitors will not influence the interaction between PD-1 and PD-L2. Accumulating evidence suggests that PD-L2 is involved in the maintenance of immune tolerance and homeostasis of several non-hematopoietic tissues and vital organs, such as lung (96-99), liver (100), kidney (101) and pancreas (102). An example is that the absence of PD-L2 resulted in significantly enhanced severity of asthma, while only minimal inflammation and the airway hyper-responsiveness were reduced in deficiency of PD-L1 (97,98,103). And thus, it has long been suspected that PD-L1 inhibitors may have a favorable toxicity profile, especially in terms of immune-related adverse effects. On the other hand, PD-L2 is demonstrated to be another crucial inhibitory receptor, and the interaction between PD-1 and PD-L2 represses the activation of anti-tumor T cell response (99,104). Several studies have reported the predictive and prognostic value of PD-L2 expression in NSCLC, independently from PD-L1 expression (105-109), and blocking the interaction between PD-1 and PD-L2 could exhibit promising anti-tumor effect (104,110). Therefore, PD-1 inhibitors, with the potencies of blocking the interactions between PD-1 with both PD-L1 and PD-L2, may induce superior efficacy. Additionally, PD-1 inhibitors are usually designed as IgG4 antibodies, which have a low affinity for C1q and Fc receptors, and thus lead to reduce the chance of antibody-dependent cell-mediated cytotoxicity (ADCC) effect (111). Conversely, PD-L1 inhibitors are generally designed as IgG1 antibodies and could elicit potent ADCC against PD-L1 expressing tumor cells and immune regulatory cells (112-114). The differences of IgG isotypes and the potency of the ADCC effect contribute to the complexity of comparison between PD-1 and PD-L1 inhibitors.

At present, there have been several published meta-analyses of indirect comparisons among different anti-PD-1/PD-L1 agents, leading to conflicting results. In some studies, PD-1 inhibitors are found to induce superior efficacy to PD-L1 inhibitors in terms of objective RR (115), PFS (116) and OS (116,117) in metastatic NSCLC, while others reported no such significant difference of treatment efficacy and patient's survival (80,118,119). Similarly, several studies indicated no significant difference in safety profiles between various PD-1 inhibitors and PD-L1 inhibitors, in terms of toxicity of any grade, immune-related AEs, AEs leading to treatment discontinuation and fatal toxic effects (116,120), but other studies found a significantly higher rate of immune-related toxicity among patients receiving PD-1 inhibitors than those receiving PD-L1 inhibitors (80,115,121,122), especially pneumonitis (121) and thyroid dysfunction (122). Additionally, even among the same type of antibodies, different drugs may have significantly different treatment efficacy and toxicity profiles, due to their distinct binding sites, various binding affinities and diverse interaction structures (111,123-125). For example, several clinical studies suggested that the PD-1 antibody pembrolizumab might have a higher rate of immune-related toxicity than another PD-1 antibody nivolumab when administered in advanced NSCLC (115,118). However, conclusions from these indirect comparisons need to be interpreted with caution as considerable biases exist. There were significant heterogeneousness and inconsistency in terms of cancer type, treatment line, biomarker expression, baseline characteristic, follow up and toxicity judgment, between different randomized clinical trials.

Up to now, durvalumab is recommended as the only PD-1/PD-L1 inhibitor among the stand care of LA-NSCLC, based on the result of the PACIFIC study. Other prospective trials are ongoing involving various kinds of other immune checkpoint inhibitors, and the best choice of PD-1/PD-L1 blockade under this indication is under debate. LUN 14-179 was a single-arm prospective phase II study that used consolidation pembrolizumab for LA-NSCLC similar to the duvalumab group in PACIFIC study, and the similar results were reported in terms of PFS and pneumonitis (126). Other anti-PD-1/PD-L1 axis agents are also being tested in the concurrent immunotherapy and CCRT mode, as described above (69,79). Although from the merely superficial numbers of these studies, PD-L1 inhibitors were safer than PD-1 inhibitors when combined with CCRT for LA-NSCLC, they are far from conclusive and needed to be further justified. In the routine clinical practice, whether the success of the PACIFIC trial can be

generalized to other anti-PD-1/PD-L1 axis agents remain unclear, but the large randomized clinical trials directly comparing different kinds of PD-1/PD-L1 inhibitors are highly warranted.

Conclusion and future directions

As immunotherapy has opened a new era in the treatment for LA-NSCLC, understanding the impact of different systematic drugs on the immune system is becoming increasingly important. Indeed, chemotherapeutics is a double-edged sword to immunotherapy, with both suppressive and stimulatory effects on the immune system. Low-dose chemotherapy has been found to enhance host anti-tumor immune response reduced toxicities, which attracted growing interest in LA-NSCLC when anti-PD-1/PD-L1 agent is involved. In consideration of the immunosuppressive effects of GCs, chemotherapy without preconditioning may be favored. When necessary, low dose GCs for a limited duration of time may be safe, while a high dose or extended duration of usage should be careful. Although CCRT followed by durvalumab consolidation is the standard of care recommended by guidelines, it is possible to improve therapeutic effects by concurrent or induction immunotherapy, and it may be critical to distinguish particular patients for different combination strategies in the future. Furthermore, several pieces of evidence suggest that PD-L1 inhibitors may have lower toxicity, while PD-1 inhibitors may induce superior efficacy. In summary, more preclinical and clinical studies are called for to look for the optimal combination of CCRT and immunotherapy for LA-NSCLC, during which the above issues need to be concerned.

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