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Review

Radiotherapy and Immunotherapy: The Power of the Teamwork for the Treatment of NSCLC

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Abstract. *Immune checkpoint inhibitors (ICPi) targeting programmed cell death 1(PD-1)/ programmed cell death ligand-1 (PD-L1) have revolutionized the treatment of patients with advanced non-small cell lung cancer (NSCLC). Despite impressive success, only a small proportion of patients benefit from PD1/PDL1 inhibitors. Radiotherapy (RT) can induce a systemic anti-tumor immune response on local and distant tumors. Some preclinical and clinical evidence showed a critical role of RT to overcome acquired resistance to immunotherapy. Currently, durvalumab consolidation represents the new standard treatment for unresectable stage III NSCLC patients whose tumors express PDL1 on ≥1% of tumor cells (TC), and whose disease has not progressed following platinum-based chemoradiotherapy (CRT). In this review, we focus on the synergic effect of RT with ICPi and the new role that different RT schedules can play in combination with immunotherapy for early-stage NSCLC.*

Currently, immune checkpoint inhibitors (ICPi) have revolutionized the treatment of patients with advanced non-small cell lung cancer (NSCLC) (1-5). Despite the encouraging success of ICPi, only a small subset of patients has an overall durable response to treatment due to tumor immune escape mechanisms causing primary resistance (6, 7). Radiotherapy (RT) can induce a systemic antitumor immune response on local and distant tumors by triggering potent immunomodulatory actions (8, 9). Herein, we review the synergist effect of RT with immunotherapy and the fundamental role the different doses, fractionations, and schedules can play on systemic antitumor immune responses in NSCLC.

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Immunotherapy and Radiotherapy: Biological Mechanisms and Antitumor Immune Response

RT plays a major role in the curative or palliative treatment of lung cancer. Stereotactic ablative radiotherapy (SABR) has been shown to be a safe and effective treatment for oligometastatic disease. Unlike standard hypofractionated RT, this non-invasive local therapy involves the delivery of a high dose of radiation (≤8 fractions with ≥5 Gy/fraction) into the targeted tumor lesions, sparing normal tissues (10). Many trials have shown the efficacy of consolidative SABR patients for stage IV oligometastatic disease (≤ 3 metastases) (11, 12). RT can activate cytotoxic signaling pathways that induce cancer cell death through DNA damage (13, 14). The cross-talk between radiation and the immune system can overcome the mechanisms of resistance of immunotherapies (15-21). Many studies have shown that combining radiation with ICPi increases local and distant tumor control (22, 23). In the phase 2 trial, PEMBRO-RT (24), patients with advanced NSCLC were randomized to pembrolizumab either alone or after stereotactic body radiotherapy (SBRT) (3 doses of 8 Gy) to a single tumor site. The overall response rate (ORR) at 12 weeks was 18% and 36% in the pembrolizumab *vs*. pembrolizumab after radiation arm (p=0.07). Median progression-free survival (PFS) was 1.9 months in pembrolizumab alone *vs*. 6.6 months (HR=0.71; p=0.19) with pembrolizumab after RT. Median overall survival (OS) was 7.6 months *vs*. 15.9 months, respectively (HR=0.66; p=0.16). Notably, the benefit of the addition of SBRT was observed only in the PD-L1–negative subgroup: (OS: HR=0.48; p=0.046 and PFS: HR, 0.49; p=0.03). In the phase I/II trial MDACC (25), NSCLC patients

with ≤4 lung or liver metastases amenable to RT plus at least one additional non-contiguous lesion were randomized to pembrolizumab with or without concurrent RT. Based on clinical feasibility, lesions were treated with SBRT (50 Gy in 4 fractions) or with traditionally hypofractionated RT (45 Gy in 15 fractions). The median PFS was 5.1 months *vs*. 9.1 months (p=0.52) for the pembrolizumab alone and pembrolizumab/ RT cohort, respectively. The ORR was 22% in the immune-RT arm and 25% in the pembrolizumab group (p=0.99). The ORR reported in non-contiguous lesions was 38% in the pembrolizumab plus SBRT group and 10% in the pembrolizumab plus hypofractionated RT group, showing activity also in unirradiated lesions (26). Different RT schedules (SBRT *vs*. hypofractionated RT) can influence the immune response due to their effect on absolute lymphocyte count (ALC) (27). Lymphocytes are radiosensitive and associated with an effective anti-tumor immune response. A decrease in ALC levels was most frequent in traditional RT regimen than SBRT (28). Moreover, compared with a hypofractionated schedule, SBRT induced superior regression of non-irradiated metastatic lesions at a distance from the primary field of treatment (abscopal effects) (29-31). The KEYNOTE-001 trial (32), showed that patients with NSCLC that received RT before pembrolizumab, achieved a longer OS (10.7 months *vs*. 5.3 months) and PFS (4.4 months *vs*. 2.1 months) when compared with patients without previous RT. Luke *et al*. (33) analyzed the activity and safety of multisite SBRT (given at doses ranging from 30 to 50 Gy) followed by at least one cycle of pembrolizumab, started within 7 days of completing of SBRT, in patients with advanced solid tumors. Median PFS and OS was 3.1 months and 9.6 months, respectively; ORR was 13.2. A recent pooled analysis of trials (34) showed that RT given within 90 days prior to ICPi in different cancers seems to be safe. Pneumonitis occurred in 6.8% *vs*. 3.8% (grade 3-4 in 1.9% *vs*. 1.1%) in RT ≤90 days *vs*. no RT groups, respectively.

Unresectable Stage III NSCLC

The encouraging therapeutic effects of ICPi were not only found in the metastatic setting. Currently, RT represents a strategic element in the management of unresectable stage III NSCLC. The definitive dose regimen for the treatment of inoperable NSCLC has been established as 60 Gy (35). In order to improve radiosensitivity of tumour cells, different platinum-based regimen were administrated with concomitant chemotherapy (36). The best concurrent CRT regimen is not yet established. Horiuchi M *et al*. (37) showed a good efficacy/tolerance ratio with cisplatin + vinorebine. The phase II, ETOP NICOLAS (38) trial, showed the safety of nivolumab combined with CRT in stage IIIA/B NSCLC. Thoracic radiation dose was 66 Gy in 33 fractions in the concurrent CRT regimen and 24 fractions in the sequential CRT regimen. Pneumonitis occurred in 42.5% and at 3 months post-RT no grade ≥3-pneumonitis was reported. The phase II trial Hoosier Cancer Research Network LUN 14-179 (39) demonstrated the safety and efficacy of consolidation pembrolizumab (for up to 1 year) following concurrent platinum-based CRT (59.4 to 66.6 Gy) in patients with unresectable stage III NSCLC. The median metastatic disease or death was 30.7 months. The median PFS and OS was 18.7 months and 35.8 months, respectively. Grade ≥2 pneumonitis was observed in 17.2% of patients. The phase II, two step trial, DETERRED (40), showed the safety and activity of atezolizumab, an anti–PDL1 antibody, with concurrent CRT. In part 1, once weekly carboplatin and paclitaxel was administered with standard course CRT (60-66 Gy) followed by consolidation with carboplatin and paclitaxel with atezolizumab for two cycles, and maintenance atezolizumab for up to 1 year. In part 2, atezolizumab was administered with concurrent CRT, followed by the same consolidation chemotherapy and maintenance immunotherapy as in part 1. In part 1, the median PFS and OS was 18.6 months and 22.8 months, respectively. Grade ≥3 overall adverse events (AE) occurred in 80% of patients (grade ≥3 immune-related AE: 30%; grade ≥2 pneumonitis: 10%). In part 2, the median PFS was 13.2 months and the median OS was not reached. The safety profile was similar to that of part 1: grade ≥3 overall AE: 80%, grade ≥3 immune-related AE: 20% and grade ≥2 pneumonitis: 16%. The phase II trial KEYNOTE 799 (41), evaluated the outcome and safety of pembrolizumab plus concurrent CRT in patients with unresectable stage III NSCLC. In cohort A, the treatment consisted of 1 cycle of carboplatin, paclitaxel, and pembrolizumab followed by carboplatin and paclitaxel weekly for 6 weeks, and 2 cycles of pembrolizumab with concurrent standard thoracic RT (60 Gy in 30 fractions). In cohort B, 3 cycles of cisplatin, pemetrexed and pembrolizumab were administrated with concurrent definitive RT. ORR was 70.5% and 70.6% in cohort A and B, respectively. Grade ≥3 pneumonitis occurred in 8.0%/6.9% of patients in cohort A/B. In the PACIFIC study (42), a phase III randomized trial, patients with stage III unresectable NSCLC who did not have disease progression after ≥2 cycles of platinum-based CRT (54 to 66 Gy), who received durvalumab, a PDL1 inhibitor, for up to 1 year, resulted in significantly longer PFS and OS than placebo. Patients were enrolled within 42 days of completing CRT. Median PFS was 16.9 months and 5.6 months (HR=0.55) for durvalumab and placebo, respectively. The 5-year PFS estimates for durvalumab and placebo were 33.1% and 19.0%, respectively. The median OS was 47.5 *vs*. 29.1 months for durvalumab and placebo, respectively (stratified HR=0.72). The 5-year OS rate was estimated as 42.9% for durvalumab versus 33.4% for placebo. The consistent OS benefit with durvalumab excluded patients with PDL1 expression on <1% of TCs (HR=1.15). The ORR was 28.9% and 18.3% in the durvalumab and placebo group, respectively. Durvalumab reduced the risk of relapse more

consistently when initiated within <14 days (HR=0.53) *vs*. ≥14 days (HR=0.78), suggesting a critical window for the first immunotherapy administration. Maximum-grade 3 or 4 AE of any cause occurred in 30.5% *vs*. 26.1% in the durvalumab group and placebo group, respectively (43, 44). A post-hoc analysis showed a durvalumab benefit in terms of PFS and OS and a manageable safety profile, regardless of age (also in patients aged ≥70 years) (45). The real-world assessment of durvalumab in patients with unresectable stage III NSCLC whose disease has not progressed after platinum- based concurrent CRT was reported in the international, observational study, PACIFIC-R (46). This real-world study showed a median PFS of 21.7 months (*vs*. 17.2 months reported for the durvalumab arm in the PACIFIC trial). PFS was higher in patients with PDL1 expression ≥1% (22.4 months) than those with PDL1<1% (16.3 months). Any grade pneumonitis was observed in 17.9% of patients. Only 35% of patients in PACIFIC-R started durvalumab within 42 days of the end of RT. The phase II PACIFIC 6 trial, evaluated the efficacy, quality of life, and safety of durvalumab *vs*. placebo in NSCLC patients who completed platinum-based sequential CRT without progression of disease or unresolved toxicities. Preliminary data showed a similar safety profile of durvalumab to that in PACIFIC trial: 88% of patients had any AE and 12% had grade 3/4 AE (47). It is interesting to underline how the occurrence of immune-related adverse events seems to be related to the efficacy of immunotherapy (48) The interim analysis of GEMSTONE 301 trial (49) showed the efficacy of sugemalimab, an anti-PDL1 antibody, in patients with unresectable stage III NSCLC who had not progressed after concurrent or sequential CRT. Median PFS was 9.0 months in the sugemalimab group and 5.8 months in the placebo arm (HR=0.64, p=0.0026). Grade ≥3 treatment-related adverse events occurred in 9% and 6% in the sugemalimab and placebo group, respectively. Pneumonitis occurred in 3% of patients in the sugemalimab group *vs*. <1% in the placebo group. Several ongoing trials are evaluating the role of immunotherapy concurrently with CRT or in the consolidative setting in unresectable stage III NSCLC: PACIFIC 2 trial (NCT03519971), EA5181 (NCT04092283), CheckMate 73L (NCT04026412), SWOG S1933 (NCT04310020).

Immunotherapy and Radiotherapy in Early-stage NSCLC

Evidence shows the activity of SABR (ranged dose from 54 to 60 Gy) for early-stage NSCLC with medical conditions precluding surgical treatment (50-52). The continuous successes of immunotherapy in the advanced setting have shifted the interest of ICPi towards early stages (53-56). Altorki *et al*. (57) in the single-center, open-label, randomized, controlled, phase II trial, compared two cycles of neoadjuvant durvalumab alone with neoadjuvant durvalumab plus stereotactic radiotherapy, in patients with potentially resectable early-stage NSCLC (clinical stages I-IIIA). In the durvalumab plus RT arm, patients received three consecutive daily fractions of 8 Gy prior the administration of the first cycle of durvalumab. Patients who completed preoperative treatment without disease progression, underwent surgical resection. Major pathological response was higher in the durvalumab combined with RT group (53.3%) than in the durvalumab monotherapy (6.7%). Grade ≥3 AE occurred in 20% *vs*. 17% of patients in the durvalumab plus RT group and durvalumab monotherapy, respectively. The selected total radiation dose administered was 24 Gy. This non-standard lower radiation dose, equivalent to a biologically effective dose of 43.2 Gy, concurrent with immunotherapy, seems to enhance the efficacy on thoracic tumors and on potential micrometastatic disease. Significantly increased major histocompatibility complex (MHC-1) gene expression was reported in patients with major pathological response after durvalumab plus RT when compared with patients without a major pathological response, and those in the monotherapy group. Lee GD *et al*. evaluated the role of the changes in PD-L1 expression and CD8+ tumor-infiltrating lymphocytes in patients with locally advanced NCSLC who underwent neoadjuvant CRT followed by surgical resection. Patients with an increased PD-L1 expression and CD8+density post-neoadjuvant concurrent CRT achieved the best outcome (58). RT generates the release of antigens during cancer cell death, upregulates immunogenic cell surface complex, and induces proinflammatory signals that trigger the innate immune system to activate tumor-specific T cells (59).

Conclusion

RT combined with ICPi showed a synergist effect on local and distant tumor control, with a good safety profile in advanced NSCLC. Currently, the multimodality treatment of unresectable stage III NSCLC involves combination CRT followed by 1 year of consolidative durvalumab in patients who do not progress after the completion of platinum-based CRT with PDL1 expression ≥1% of TCs and without unresolved toxicities. The optimal timing window of PD1 or PDL1 inhibitors with RT remains elusive. The preliminary results that emerged from recent clinical trials in early-stage disease, seem to suggest the preoperative short-course SBRT and immunotherapy as a novel therapeutic strategy.

Conflicts of Interest

The Authors declare no conflicts of interest in relation to this study.

Authors' Contributions

Conceptualization, M.B. and A.C.; methodology, M.B,A.C.; validation, M.B, S.R, M.Z. and A.C.; formal analysis, M.B, A.C.;

investigation, M.B.; resources, M.Z.; data curation, M.B, S.R, M.Z. and A.C.; writing – original draft preparation, M.B,A.C writing – review and editing, M.B, S.R, M.Z. and A.C.; visualization, M.B, S.R, M.Z. and A.C.; supervision, A.C.; Authors have read and agreed to the published version of the manuscript.

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