RESEARCH ARTICLE

PD (L) 1-Inhibitors and Radiation: A Good Combination for Local and Systemic Effects?

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Abstract:

Radiation therapy is an important component in treatment of solid tumours, in a locally advanced situation and also in a metastatic situation. Indications for using PD- (L) -1 inhibitors increase especially in the metastatic situation, but also in locally advanced solid tumours. Preclinical data show local and systemically effective synergies between local irradiation and an application of checkpoint inhibitors. In the metastatic situation, a possible abscopal effect is of particular interest. This abscopal effect can be achieved especially in concurrent approaches of PD-(L)-1-inhibitors and stereotactic radiation with higher single doses like 3 x 8 Gy or 4 x 12,5 Gy. In locally advanced tumours a local enhancement of the radiation effect, and also an abscopal effect to eliminate potential micrometastases to is of great interest to achieve healing. In this treatment situation promising results are seen in the application of PD-(L)-1-inhibitors as maintenance after concurrent chemoradiation especially in non-small cell lung cancer, as well as in concurrent applications of conventionally fractionated radiotherapy and PD-(L)-1 inhibitors. These approaches and results are considered from the clinician's point of view.

Introduction:

In the treatment of solid tumours, radiation therapy (RT) is an essential component. In the curative situation, solid tumours can be treated curatively by radiation therapy alone or in combination with chemotherapy especially as concurrent chemoradiation (RCT) aimed to preserve organ prevention and organ function. In the palliative treatment situation, radiation therapy also has an important function in symptom control and thus in improving quality of life. In the oligometastatic treatment situation, a curation can even be achieved in combination with medical tumour therapy and consistent local therapy on the primary tumour and all metastatic sites.

In the relapse situation as well as in the palliative situation, especially in the first-line situation, the importance of checkpoint inhibitors, in particular PD-1 inhibitors and PD-L-1 inhibitors, is growing. PD-(L)-1-Inhibitors can be used as monotherapy or in combination with chemotherapy and ongoing maintenance. The survival data significantly improved with PD-(L)-1-inhibitors, and showed less side effects than chemotherapy. Also in the treatment situation of local advanced solid tumours, more studies with PD-(L)-1-inhibitors are ongoing and already published.

In palliative situation as well as in curative situation, the question of a possible and effective combination of RT and immunotherapy is becoming increasingly important, achieving local and systemic synergies (abscopal effect) regarding to possible increased side effects for the patients.

The aim of this article is providing a general overview for clinicians on radiobiological and immunological rationale for combining RT and PD- (L) -1 inhibitors, as well as useful clinical approaches and published results.

Preclinical rationale for combining RT and PD-(L)-1-Inhibitor

RT has a great influence on tumour microenvironment as well as on immune system. Best known is certainly an immunosuppressive effect, caused by a radiation therapy-induced leukopenia, whereby the number but not the function of immune cells is temporarily reduced. (Modi et al, 2021; Rückert et al, 2021).

Irradiation causes DNA double-strand breaks in tumour cells, and further damages, which are irreparable for tumour cells. This leads to a release danger proteins (DAMP) and to an increased expression of MHC class 1 surface proteins. This effects increasing phagocytosis activity by dendritic cells. These dendritic cells present tumour-derived antigens to T-cells, and the adaptive immune response is activated, which leads to a multiplication of the activated tumour-specific T-cells and their release into the blood.

In this phase, the activation is checked and controlled by the CTLA-4 checkpoint, which can be positively influenced by CTLA-4 inhibitors. The activated tumour-specific T-cells can then be active in the primary tumour but also at other tumour locations as metastases, which is described as the abscopal effect. These described processes can be viewed as in situ vaccination of the tumour by radiation therapy (Liu et al, 2018; Candeias et al, 2016).

The primary irradiated tumour and other primary non-irradiated tumour lesions can interact with the programmed death ligand 1 (PD-L 1), which can inhibit the activity of the activated tumour-specific T cells. In this situation a PD- (L) 1 inhibitor can inhibit this inhibitation and so significantly increase the

activity of the activated tumour-specific T-cells to combating tumour cells. (Modi et al, 2021; Rückert et al, 2021). This local increase in effectiveness of radiation therapy and PD-L-1 inhibitor as well as the abscopal effect in the combination of radiation and PD-L-1 inhibitor could be impressively demonstrated in mouse model (Deng et al, 2014).

Also in a mouse model, Frey and colleagues (Frey et al, 2017) showed an increase in immunocompetent cells after 4 to 7 days in irradiated tumours, so that the working group recommends starting RT on Wednesday and applicate PD- (L) -inhibitors on Friday after the RT fraction.

The abscopal effect is of particular interest in everyday clinical practice, especially in the metastatic situation. However, to achieve an abscopal effect, a number of prerequisites are necessary, which have yet not been clarified in vivo. Beside a special chronological order between RT and application of a PD-(L)-1-inhibitor, the height of the Radiation fraction dose plays an important role. Single dose RT with a high fraction dose like in radiosurgery and doses over 8 Gy seem to have less favourable abscopal effects.

Also in a mouse model Grapin (et al, 2019) showed by different radiation schedules (18x2Gy; 3x8Gy; 1x16,4Gy) with an equal biological effectivity, the same local control but with the addition of a PD-1 inhibitor, the response in not irradiated tumours only improved significantly in the 3x8Gy group.

Other in vitro tests also show different immune responses in irradiated tumours compared to non-irradiated tumours, and also the concentration of immunocompetent cells is different. So even in mouse models no optimal schedule is known in combination of RT and PD-(L)-1-inhibitor to achieve an abscopal effect, which could transferred into patient treatment strategies (Modi et al, 2021; Rückert et al, 2021).

Combination of radiation and PD- (L) -1 inhibitors in the metastatic situation and the search for the abscopal effect

Potential side effects in combination of Radiation and PD-(L)-1 Inhibitor:

From combination of radiation and chemotherapy it is known, that there should be no overlapping toxicity with concurrent chemotherapy in the area of the radiation field. This principle also applies in principle to the combination of irradiation with checkpoint inhibitors, whereby there are no substance-typical and dose-dependent side effects, like known form chemotherapy, but there are possible side effects in all organ systems of the body at all. Nevertheless, checkpoint inhibitors are generally well tolerated. A meta-analysis (Jing et al, 2021) shows grade III / IV toxicities in women in 18.3% and in men in 26.3% when PD- (L) -1 inhibitors are given as monotherapy. Unfortunately, especially in phase III trials, only 26% of the trials report toxicity data (Barhli et al, 2021).

For combination RT with PD-(L)-1-inhibitor, side effects in the lung, in the gastrointestinal tract and in the neurocranium are of particular importance.

Potential side effects in lung, specifically pneumonitis, is best documented in the so-called PACIFIC trial (Antonia et al, 2017). In NSCLC stage III, after chemoradiotherapy a maintenance with durvalumab versus placebo was randomized. The rate of pneumonitis of all grades was 33.9% in the durvalumab arm and 24.8% in the placebo arm, and clinically relevant grade III / IV pneumonitis was comparable with 3.4% versus 2.6%. In the NICOLAS trial (Peters et al, 2019), a phase II study in NSCLC stage III, with chemoradiation and concurrent application of nivolumab, which was also administered as maintenance, a pneumonitis rate grade III or

higher was seen in 10% (8/80) of patients. Assuming that radiogenic pneumonitis occurs within 3 months after end of RT, then only in 5% (4/80) of patients a pneumonitis was recorded, which is within a scope of grade III pneumonitis even without parallel administration of nivolumab. In a retrospective analysis (Cousin et al, 2021), so-called recall phenomena due to previous irradiation were described if later PD-(L)-1-inhibitors were applicate. In this analysis a rate of pneumonitis grade III was seen in 15/80 patients (18.75%). Since these data were collected retrospectively and the diagnosis of pneumonitis is primarily based on computer tomographic imaging, these data should certainly be interpreted with caution, but should be noted.

Data on colitis as side effects in combination RT and PD- (L) -1 inhibitors are rare. From our own clinical experience, irradiation of bone metastases in the lower thoracic spine and lumbar spine as well as stereotactic body radiation of adrenal metastases together with PD- (L) -1 inhibitors are rather unproblematic, since these are also relatively small intestinal volumes that receive a corresponding radiation dose. Other reports are being made in a phase I study on organ-preserving therapy for urothelial carcinoma of the urinary bladder (Marcq et al, 2021). After transurethral resection, patients were treated with chemoradiation (RCT) (2 Gy to 40 Gy, lymphatic nodes, 2.5 Gy to 50 Gy urinary bladder) simultaneously with gemcitabine (100 mg / m2, weekly) and atezolizumab. In the standard dosage of 1200mg i.v., dose limiting toxicities occurred in 3/5 patients, mainly colitis. A dose reduction of atezulizumab to 840 mg i.v. reduced toxicity, but also 4/8 patients developed grade III colitis, mostly shortly before end of RCT, so that this study was interrupt due to unacceptable toxicities. It certainly needs to be questioned whether RCT with gemcitabine is an optimal treatment schedule in bladder cancer, however it still should be noted, that in this treatment situation a larger intestinal volume is irradiated than in body stereotactic radiation. This should be considered when combining RT and PD-(L)-1-inhibitors in treating tumours of the pelvic.

Stereotactic irradiation of brain metastases in combination with checkpoint inhibitors is certainly one of the first treatment situation in which RT and Checkpoint inhibitor was applied in a combination. Data on negative interactions and side effects, in particular on the occurrence of brain necrosis, are rare and all retrospective. One of a larger systematic retrospective evaluation (Chen et al, 2018) of 260 patients with 623 brain metastases showed no difference in acute neurological toxicity such as headache, nausea, and vomiting between stereotactic radiation alone, checkpoint inhibitors applicate after stereotaxic radiation, or concurrent application of RT and checkpoint inhibitor. There were also no significant differences in late toxicity, in particular in occurrence of brain necrosis. The average rate of brain necrosis was 3%. A current analysis (Enright et al, 2020) of 77 patients with NSCLC and 132 brain metastases, which also retrospectively compares stereotaxic radiation alone and with a concurrent application. This showed 6% brain necrosis in the combination arm and 11.3% brain necrosis in the stereotaxic arm. Therefore a combination of RT and (concurrent) application of PD-(L)-1-inhibitor can be considered safe and feasible.

In summary, the combination of RT and PD-(L) -1 inhibitors can be considered safe. This is also underlined by the first results of two randomized studies from the ASCO 2018. In treatment with PD-1 inhibitors with or

without RT in metastatic NSCLC (Theelen et al, 2018) and metastatic HNSCC (McBride et al, 2018) no increased grade III/IV toxicities were observed.

Retrospective analyses of combination RT and PD- (L) -1 inhibitor focused on local control and systemic effects:

The first systematic retrospective analysis on effectiveness in combination RT and checkpoint inhibitors were done in the treatment situation of brain metastases. A larger retrospective analysis was done by Chen (et al, 2018) in patients with brain metastases from NSCLC, malignant melanoma, and renal cell carcinoma. Stereotactic radiation alone was applied in 181 cases, RT and sequentially application of checkpoint inhibitors were seen in 51 cases and RT and concurrent checkpoint application were seen in 28 cases. The local control with usually one-time irradiation of 20Gy was almost identical in all groups (12-month control: 82%: 79%: 88%). The median number of new intracerebral metastases was 4 in the first two groups and 2 in the concurrent group. The median survival after diagnosis of brain metastases was 12.9 months versus 14.5 months versus 24.7 months, i.e. significantly higher in the concurrent group ($p = 0.002$). Since the distribution of prognostic factors in the three groups was comparable, this result underlines the consideration of positive systemic interactions of the concurrent application of RT and checkpoint inhibitors.

Enright (et al, 2021) and colleagues showed similar results in patients with brain metastases in NSCLC. Here 44 patients with 68 brain metastatic lesions were given stereotactic radiation alone, all of whom received chemotherapy within an interval of 3 months, while the other group with 33 patients (64 lesions) received stereotactic radiation of the brain metastases together with immunotherapy. Again, there were no significant differences in prognostic factors. Local control after 2 years was 97% in the combination group and 86% in the stereotaxic RT group alone ($p = 0.046$). After 2 years, new intracerebral lesions appeared in 38.6% and 66.5% ($p = 0.02$), respectively. The 2-year survival was 62% and 35%, respectively ($p = 0.023$).

Comparable analyses of lung or liver metastases are not published in this detailed form. An overview of combination RT and checkpoint of various metastatic tumour entities, mostly with concurrent application of hypofractionated radiation therapy and PD- (L) -1 inhibitors (Mohamed et al, 2018) shows overall response rates of 28%, with 10% complete remission, whereby the response of bone metastases was worse. The combination RT of lung metastases and checkpoint inhibitor was significantly more associated with a complete remission. It cannot be clarified whether this is due to a better immunogenicity of the lung, or a generally higher biological equivalent radiation dose in lung metastases than in bone metastases, or it is a mixture of both reasons. Of interest is in this context a meta-analysis on combination of checkpoint inhibitors and RT (Xu et al, 2020), which shows a significant improvement in survival in the combination RT and checkpoint inhibitor compared to checkpoint inhibitor or radiotherapy alone.

A retrospective analysis of patients with malignant melanoma (Klemens et al, 2019) treated with checkpoint inhibitors, examined a potential benefit of the combination with additional radiation therapy from the point in time. Patients who are additionally irradiated in the case of persistent metastases (1-3 lesions) benefit more from RT than patients

irradiated for new grown lesions (1-3). The 3-year PFS was 70% and 6% (p = 0.001).

Results of prospective studies:

Prospective randomized studies in the metastatic situation to show an possible abscopal effect by concurrent RT and PD-(L)-1-inhibitor application are still mostly in recruiting. In most studies, RT is only applied to one lesion for "in situ vaccination" and looking for the abscopal effect.

In one of the first randomized phase II study, 76 patients with NSCLC and progressive metastatic disease after chemotherapy were included (Theelen et al, 2019), 40 patients received pembrolizumab alone and a 36 patients had previously received stereotactic RT of one lesion with 3 x 8 Gy. The primary endpoint of this study is overall response rate (ORR) after 12 weeks, secondary endpoints are survival. Unfortunately, the study did not stratify to expression of PD-L-1, so 66% were PD-L-1 negative in the pembrolizumab arm alone and only 50% in the concurrent RT arm. The ORR was 18% versus 36% (p = 0.07) in favour of the irradiated group. The median progression free survival (mPFS) was 1.9 months versus 6.6 months, the median overall survival (mOS) was 7.6 months and 15.9 months in favour of concurrent stereotaxic RT. Interestingly, in particular PD-L-1-negative patients benefited from the additional stereotaxic RT, which can underline the positive immunomodulatory effect of RT.

At the ASCO 2020, Welsh (et al, ASCO 2020) presented first pooled data from two randomized studies in metastatic NSCLC with pembrolizumab alone (n = 66) or with RT of one lesion (n = 65). The primary endpoint of the study was ORR outside the radiation field as a measure of the abscopal effect due to the additional RT. The ORR was 21 vs. 35% (p = 0.01) in favour of the additional RT of one lesion, mPFS was 4.4 months vs. 8.3 months (p = 0.046) and mOS was 9.2 months vs. 19.2 months (p = 0.04). The fractionation of RT which the strongest absolute effect, measured by the ORR outside the radiation field, was observed with 3x8 Gy (ORR 48%) and 4 x12.5 Gy (ORR 54%) compared to pembrolizumab alone (ORR 20%) and 15x3 Gy with ORR comparable to pembrolizumab alone.

In their publication (Welsh et al, 2020) the group refers to the results of a phase I / II study with a total of 100 patients who either received pembrolizumab alone or with RT of one lesion (4x 12.5 or 15x3 Gy). The ORR was 22% with pembrolizumab alone, 38% with pembrolizumab and 4 x 12.5 Gy, and 10% with pembrolizumab and 15 x 3Gy. The mPFS was 5.1 months compared to 9.1 months with concurrent RT. Interestingly, also in this study, patients with a lower PD-L-1 expression more benefited from the concurrent RT. With low PD-L-1-expression, mPFS was 4.6 months versus 20.8 months in favour for concurrent RT (p = 0.004).

In metastatic urothelial carcinoma, Sundahl (et al, 2019) published a small phase I study with sequential irradiation (3 x 8 Gy on one lesion) followed by pembrolizumab versus the same irradiation concurrent with pembrolizumab. Response rates (RECIST v1.1) of 0% and 44% and a mOS of 4.5 months to 12.1 months were observed. These data also support the concurrent application of RT and PD- (L) -1 inhibitor.

Study approaches for oligometastatic tumour situations combining PD- (L) -1 inhibitors and local RT of the primary tumour and all metastasis lesions (max. 5) are currently not known. An analysis by Schubert and colleagues (Schubert et al, 2020),reports 50 patients with different tumour entities, mostly metastatic NSCLC and HNSCC, all treated

with a combination of checkpoint inhibitors and RT, shows that these considerations could be useful for patients. In 27 patients all lesions were irradiated, in 23 patients only one lesion was irradiated. The mPFS is 11.6 vs. 4.2 months ($p < 0.001$), the median time to progression (mTTP) has not yet been reached in the group of completely irradiated tumour lesion patients; in the other group it mTTP was 4.6 months ($p = 0.028$), the mOS is 11.6 vs. 4.2 months ($p = 0.007$).

In summary, the concurrent application of stereotaxic RT and PD- (L) -1 inhibitors, improve response locally and systemically and show promising survival data. As is known from the preclinical data, higher single doses in a fractionated RT are obviously more immunologically effective than a single dose of 3 Gy in fractionated RT. Likewise, patients with lower PD-L-1 expression probably benefit significantly more from the combination of RT and PD- (L) -1 inhibitor, which also underline the immune-modulating effect of (stereotactic) RT.

Combination of radiation and PD- (L) -1 inhibitors in locally advanced tumours: with or without chemotherapy?

For most locally advanced solid tumours, concurrent RCT is the standard treatment. These results could not be improved by more cycles of chemotherapy, for example as induction chemotherapy or maintenance chemotherapy. Changing potentially more toxic chemotherapy to a probably better tolerated systemic drug such as EGFR receptor antagonists (for example cetuximab) concurrent to RT did also not show any equivalent survival data.

Whether integrating PD- (L) -1 inhibitors into the concept of definitive concurrent RCT can improve treatment results has already been proven in some studies and is still part of a large number of studies. In principle, the PD- (L) -1 inhibitors can be integrated into the treatment concept of concurrent RCT as maintenance therapy after RCT, or directly into the RCT-schedule or, instead of chemotherapy, applied concurrent to RT and followed by a maintenance.

PD- (L) -1 inhibitor after definitive chemoradiotherapy as a maintenance:

The rationale for maintenance is a consolidating of the local treatment result for perhaps also a better local control, and to reduce the number of potential not by imaging detectable micrometastases to improve PFS and OS.

This approach was successfully pursued in the so-called PACIFIC trial (Antonia et al, 2017) in patients with NSCLC stage III after definitive RCT. The maintenance of durvalumab improve local response rate compared to placebo and reduce local and systemic progression. The median time to death of distant metatsases was significantly increased from 16.2 months to 28.3 months (Antonia et al, 2018). Overall, a significant improvement in mPFS was achieved from 5.6 months to 16.6 months and the 4-year overall survival increased from 36.3% to 49.6% (Faivre-Finn et al, 2021). A series of so-called real world data analyses are able to confirm these positive effects of maintenance of durvalumab (Taugner et al, 2021). The positive effect of durvalumab is significantly greater, if time interval between the last irradiation and the first administration of durvalumab is not greater than 14 days, which underlines the positive interactions between RT and PD- (L) -1 inhibitors. This approach can also be useful for many other solid tumours also with regard to a possible upregulation of PD-L-1 receptors through radiation.

Integration of PD- (L) -1 inhibitors in concurrent chemoradiotherapy schedules and subsequent maintenance:

This approach aims even more to an enhancement of effects between RT and chemotherapy and PD- (L) -1 inhibitors. The problem is the complexity of the combination of these three components and the total effect on tumour. One open question is the optimized sequence of the three components, and the risk that positive effects of the combination of two of the components can result in a negative effect with the third component. In relation to RT, the (platinum-based) chemotherapy should be applied shortly before RT and PD-(L)-1-inhibitor should be applied after radiation. In the combination of chemotherapy and immunotherapy, there are also some arguments in favour of this sequence, first chemotherapy than PD-(L)-1-inhibitor, but this is not the usual schedule in chemo-immunotherapy. For example, a single course of induction chemo immunotherapy as part of the CHECK-RAD study (Hecht et al, 2020) in locally advanced head and neck tumours, checkpoint inhibitors follow a chemotherapy of docetacel and cisplatinum. This induction chemo-immunotherapy achieved histologically proven rates of complete remissions of 48%, certainly a significantly higher response rate than in first-line therapy schedules of chemo-immunotherapy, which start with the checkpoint inhibitor followed by chemotherapy.

The considerations above can prove to be true in the results of the NICOLAS trial (Peters et al, 2019), a phase II study in NSCLC stage II, integrating nivolumab in the schedule of concurrent RCT and maintenance of nivolumab. The primary endpoint was increasing the 1-year PFS from 45% to 60%. After a median follow-up of 21 months, the 1-year PFS is 45%, the mPFS 12.7 months and the mOS 38.8 months. These survival data here are not better than survival data of the PACIFIC trial (Antonia et al, 2018), they are even worse, although there is still a lack of randomized data on this approach, as well as a lack of more phase II studies. In addition to NSCLC, studies are currently recruiting mainly for cervical carcinoma or HNSCC. But in locally advanced HNSCC, the JAVELIN 100 Head and Neck Cancer Study (RCT alone versus RCT together with atezolizumab, including maintenance) was stopped because the planned primary study endpoint of improving PFS could no longer be achieved according to an independent committee.

PD- (L) -1 inhibitor with radiation therapy instead of chemoradiotherapy:

This therapeutic approach could be of interest for older patients and chemotherapy-unfit patients, as well as in the sense of a therapy deescalation to reduce toxicity, with at least the same local and systemic effectiveness.

A small phase II study of 29 patients with local advanced HNSCC for whom cisplatin was contraindicated shows first positive results. Patients received a total of 6 courses of pembrolizumab in the usual dosage, pemborlizumab starting concurrent with RT (Weiss et al, 2020). The primary study endpoint was mPFS greater than 16 months. After a median FU of 21 months, mPFS was not yet reached, the 2-year PFS is 71% and the 2-year OS 75%.

In the CheckRad-CD8 study (Hecht et al, 2020), patients who show an increase in CD-8 cells in tumour after a course of chemo-immunotherapy are treated with radio-immunotherapy (durvalumab) and a maintenance. As already mentioned, high rates of complete remissions after induction therapy of 48% are achieved. The patients with radioimmunotherapy achieve a 2-year

PFS of 73% and a 2-year OS of 86% (Hecht et al, submitted 2021).

Further study approaches to this question after these promising results are desirable.

In summary, for locally advanced tumours local and systemic synergies can be seen mainly in the combination approach of PD-(L)-1-inhibitor after RCT. The results to concurrent application of conventionally fractionated radiotherapy and PD- (L) -1 inhibitor are also very promising, while the approach PD-(L)-1-inhibitor integrated in the chemoradiation schedule is not yet very convincing.

Conclusion:

The combination of RT and PD (L) -1 inhibitor offers promising therapeutic results in terms of local and systemic control in the various approaches and tumour situations, without more toxicity. For the metastatic situation, concurrent approaches of stereotactic RT (3x8 Gy or 4x12.5 Gy) and PD-(L)-1-inhibitors probably are more effective than a usual palliative fractionation with 3Gy single dose. In the treatment of locally advanced solid tumours, the maintenance of a PD- (L) -1 inhibitor after RCT offers the most established combination approach, especially in NSCLC. Very promising appears the combination of conventionally fractionated radiotherapy with a concurred PD-(L)-1-inhibitor in locally advanced solid tumours.

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