Therapeutic Approaches of Radioresistance in NSCLC

Subjects: Cell Biology

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Survival in unresectable locally advanced stage non-small cell lung cancer (NSCLC) patients remains poor despite chemoradiotherapy. Adjuvant immunotherapy improved survival for these patients but it is still far from curing most of the patients with only a 57% survival remaining at 3 years. This poor survival is due to the resistance to chemoradiotherapy, local relapses, and distant relapses. Several biological mechanisms have been found to be involved in the chemoradioresistance such as cancer stem cells, cancer mutation status, or the immune system. New drugs to overcome this radioresistance in NSCLCs have been investigated such as radiosensitizer treatments or immunotherapies. Different modalities of radiotherapy have also been investigated to improve efficacity such as dose escalation or proton irradiations.

Keywords: non-small-cell lung cancer ; cancer stem cell ; radiotherapy ; Radioresistance

1. Introduction

Lung cancer was the leading cause of cancer mortality worldwide in 2015 with 1.6 million deaths [1]. Non-small cell lung cancer (NSCLC) is the most common histological form accounting for 80% of all lung cancers. Among patients with NSCLC, approximately 35% are at a locally advanced unresectable stage with the overall survival at 5 years remaining low at approximately 10 to 15% despite treatment with radiotherapy combined with chemotherapy [2]. Recently, adjuvant Durvalumab immunotherapy improved overall survival for unresectable stage III NSCLC patients responding to chemoradiotherapy [3]. However, even in this selected population, the overall survival at 3 years was 57% [4].

The TNM staging is the current main prognosis factor of survival in stage III unresectable NSCLC treated by chemoradiotherapy but others factors such as WHO performance status, gender, number of positive lymph node stations, gross tumor volume, clinical T stage, chemotherapy, radiation therapy overall treatment time, and radiotherapy dose could be involved in the prognosis [5].

The mutational status in driver genes such as epidermal growth factor receptor (EGFR) mutations, Kirsten rat sarcoma viral oncogene (KRAS) mutations, or anaplastic lymphoma kinase (ALK) translocations or mutations could drive the prognosis for stage III unresectable NSCLC treated by chemoradiotherapy [6][7][8][9][10]. However, despite these potential mutational status prognoses, there are few biological mechanisms clearly recognized explaining radiotherapy failure for stage III NSCLC.

In the recent decades, cancer stem cells or cancer initiator cells (CSCs) have been described as a possible origin of aggressive characteristics of cancers with properties of self-renewal, metastasis formation, and resistance to treatments [11].

2. Dose Escalation and Dose Painting in Radiotherapy

Conventional radiotherapy associated with concomitant chemotherapy based on platinum is the standard treatment for inoperable stage III NSCLC patients. Radiotherapy in this indication usually delivers 60 to 66 Gy in 30 to 33 daily fractions of 2 Gy [2]. A phase III trial in unresectable stage III NSCLCs tried to overcome radiation resistance by escalating the dose at 74 Gy with an unexpected result due to toxicity: survival was worse in the patient group treated with 74 Gy than in the patients group treated with 60 Gy [12]. An escalating dose (from 70 to 90 Gy) increased cardiac toxicity and reduced survival despite the antitumor benefit [13]. However, clinical studies have reported contradictory results and some studies showed better survival with an individually adapted escalating dose (84–102.9 Gy) approach based on predictive irradiated lung tissue volumes [14]. Despite this personalized approach in escalating dose, survival remains poor with high toxicity. Heterogeneous dose distribution guided by predictive markers of local radioresistance in the tumor might represent the future of escalating schemes of radiotherapy. Several clinical studies have investigated the efficacy of a limited escalating dose (boost) guided by PET imaging (RTEP studies). A RTEP7 study is currently investigating the use

of a boost up to 74 Gy, limited to the tumor region remaining [^{18}F]FDG hypermetabolic after 42 Gy (NCT02473133). This approach is named dose painting or biologically-guided dose painting. [^{18}F]FMISO appeared to have a different distribution without any correlation with [^{18}F]FDG and might conduce to different approaches of targeting hypoxia tumor regions [15][16].

3. Concomitant and New Radiosensitizing Treatments

Since now, only chemotherapies based with platin salts are the concomitant treatments associated with radiation therapy to treat unresectable stage III NSCLCs [2][17]. The additive or synergistic effect as a radiosensitizer of platin salts is debated and the radiosentive effect could be explained with implication of the ATM pathway [18]. Cisplatin was reported to radiosentize in vitro in an NSCLC cell line such as H460 and to have no effect on other NSCLCs such as A549 [18]. Several mechanisms could explain platin salt resistance in NSCLCs such as the reduced intracellular accumulation of cisplatin, the enhanced drug inactivation by metallothionine and glutathione, the increased repair activity of DNA damage, and the altered expression of oncogenes and regulatory proteins [19]. New therapies targeting DNA damages repair pathways such as poly(ADP-ribose) polymerase inhibitors (PARPi) could enhance the response to chemoradiotherapy in NSCLC. The poly(ADP-ribose) polymerase (PARP) are proteins implicated in the recognition and repair of DNA damages [20]. So PARP inhibitors induce cell mortality by the accumulation of DNA damages and act as a radiosensitizer in many in vitro and in vivo studies on several cancer cell lines including NSCLC [21]. The PARPi radiosentisation ratio was comprised between 1.1 and 1.62 in normoxia (21% O_2) and could reach 2.87 in hypoxia conditions (1% O_2) in xenograft models [22]. PARPi and platin salts could also synergize in NSCLC [23]. So PARPi might represent an interesting association in chemoradiotherapy for unresectable stage III NSCLCs, as suggested by a phase 2 clinical trial with Veliparib [24]. Furthermore, PARPi alone or in association with radiation therapy could activate the antitumor immune response and synergize with immunotherapies [25]. The association between a PARPi such as Niraparib and radiation showed the activation of the antitumor immune response in NSCLCs with an increase in CD8+ T lymphocytes, the activation of the STING/TBK1/TRF3 pathway, and the expression of chemokines such as CCL5, CXCL10, and cytokines such as interferon β [26]. However, PARPi can induce hematologic toxicity such as neutropenia, limiting its association with chemotherapy [27]. Nanoparticles administration of PARPi can improve diffusion to the tumor due to their passive targeting ability on tumor tissue that has an enhanced permeation and retention effect [28][29][30]. Therefore, PARPi nanoparticles could enhance the radiosensitizing effect in NSCLC [31].

4. Concomitant Immunotherapy

Radiotherapy can induce either immunosuppression or an antitumor immune response depending on various parameters. Radiotherapy in a large field including lymph nodes and vessels has been reported to induce lymphopenia in NSCLCs, depending of the radiation dose and the radiation volumes [32][33][34]. This radiation impact on the T lymphocytes, particularly with the daily fraction scheme of 2 Gy, can induce more failure in disease control due to an immunosuppressive effect [35]. Hypofractionated radiotherapy with high dose per fraction (6 to 10 Gy) such as stereotactic radiotherapy for early stage NSCLCs, appeared to stimulate the immune response with immunogenic cell death better than conventional radiotherapy with 2 Gy daily fractions [36]. Hypofractionated radiotherapy in unresectable stage III NSCLCs delivers 55 to 66 Gy in 20 to 24 fractions of 2.75 Gy for example [37][38]. This schedule of radiotherapy could not induce the same effect as stereotactic radiation that can spare more healthy tissues. Furthermore, conventional radiotherapy could upregulate PD-L1 in NSLCs [39][40][41]. Concomitant immunotherapy might counterbalance this immunosuppressive effect of chemoradiotherapy, in particular anti PD-1 immunotherapy, as suggested in NSLC mice models [39][40][41]. AIRING (Accelerated Radio-Immunotherapy for Lung Cancer) is a phase II clinical trial that is currently investigating the potential association Nivolumab (an anti PD-1 immunotherapy) in association with radiotherapy for patients who are not eligible for concomitant chemotherapy (NCT04577638). However, concomitant immunotherapy, in particular anti CTLA-4 immunotherapy (Ipilimumab), can increase pulmonary toxicity [42]. Consolidation anti PD-1 immunotherapy (Pembrolizumab) did not increase toxicity in a phase 2 trial [43] and consolidation anti PD-L1 immunotherapy (Durvalumab) was well tolerated despite a slight increase in pulmonary toxicity in the PACIFIC phase 3 trial [3], encouraging the use of immunotherapy targeting the PD-1/PD-L1 axis with chemoradiotherapy.

5. Adjuvant Immunotherapy

Immunotherapy can also be used as a maintenance therapy after the end of the chemoradiotherapy treatment. One of the first trials assessing maintenance therapy with an immunotherapeutic agent is the cohort number four of the NCT00455572 trial, in which patients presenting with cancer/testis antigen MAGE-A3-positive NSCLCs received intramuscular injections of MAGE-A3 with the immunostimulant agent AS15. MAGE-A3 is considered cancer-specific

because the physiological cells expressing it, i.e., spermatogonia and trophoblasts, cannot present epitopes because of the lack of major histocompatibility complexes on these cells' membranes. After injections, all the patients of the cohort were seropositive for MAGE-A3-specific antibodies vs. 1/12 patients at baseline and 5/6 and 2/6 assessable patients that had MAGE-A3-specific CD4+ and CD8+, respectively, T-cells. Efficacy has not been reported for this trial but a lack of efficacy using the same agent in a different setting mandated the discontinuation of the investigations of this therapeutic [44].

Tecemotide, a synthetic lipopeptide derived from the mucin 1 (MUC1) sequence, was assessed as a maintenance therapy for MUC1-positive NSCLCs after chemoradiotherapy, as it was shown to induce a T-cell response in preclinical models and in patients. The START trial (Stimulating Targeted Antigenic Response To non-small-cell lung cancer) was a phase 3 trial that randomized MUC1-positive NSCLC patients with at least a stable disease after the initial chemoradiotherapy between maintenance tecemotide vs. a placebo. The trial failed to achieve its primary endpoint with a median overall survival (OS) of 25.6 months for tecemotide versus 22.3 months for placebo (HR = 0.88; $p = 0.123$) [45].

Durvalumab, an anti-PD-L1 antibody, has been assessed in the PACIFIC study, a phase 3 trial evaluating maintenance with durvalumab for 1 year versus a placebo. The trial showed improved progression free survival (PFS) (16.8 vs. 5.6 months) [3] and OS (28.3 vs. 16.2 months) [46] favouring the durvalumab arm. These results were confirmed with an updated 4 years OS rate of 49.6% for the durvalumab arm versus 36.3% for the placebo arm [47]. Subgroup analysis showed that PDL-1-positive patients tend to derive more benefit from this treatment than PDL-1-negative patients. Durvalumab maintenance therapy is now part of the standard of care for stage III NSCLC patients who have at least a stability after chemoradiotherapy.

Other anti-PD-1 agents such as Nivolumab and Pembrolizumab have been tested in smaller phase 2 trials. Nivolumab has been assessed in the NICOLAS trial in concomitance with chemoradiotherapy and in maintenance for a maximum of 1 year if the patient did not progress at the end of it. Seventy-nine patients were enrolled, the median PFS and OS were 12.7 months and 38.8 months, respectively [48]. A randomized phase 3 study versus a placebo was designed but only eight patients were randomized because of the publication of the PACIFIC study and giving a placebo to the patients was deemed unethical [49]. Pembrolizumab has been assessed in the HCRN LUN14-179 trial as a maintenance therapy for a maximum of 1 year after chemoradiotherapy for patients with stage III NSCLC. A total of 93 patients were enrolled, the median PFS and OS were 18.7 months and 35.8 months, respectively (NCT02343952). There is a randomized versus placebo phase 2 trial ongoing in Italy (NCT03379441).

Immunotherapies can also be used in association to try to prevent secondary resistance to immunotherapy maintenance. COAST is a phase 2 trial that randomized in a 1:1:1 manner patients between durvalumab alone or in association with oleclumab, an anti-CD73 monoclonal antibody, or monalizumab, an anti-NKG2A monoclonal antibody, for up to 12 months of treatment. Median PFS was 6.3 months for durvalumab alone, 15.1 months (HR = 0.65) for the durvalumab + monalizumab arm, and not reached (HR = 0.44) for durvalumab + oleclumab [50]. These first results have to be analyzed with caution as the durvalumab alone arm compares poorly with the results of the PACIFIC trial.

Finally, PD-1 inhibitors can be used in association with anti-TIGIT antibodies. Ongoing phase 3 trials such as KEYVIBE-006 (NCT05298423) and SKYSCRAPER-03 (NCT04513925) compare durvalumab with the combination of pembrolizumab and vibostolimab or the combination of atezolizumab and tiragolumab, respectively, for up to 12 months of treatment.

6. New Irradiation Techniques: Hadrontherapy

One of the simplest ways to combat tumor radioresistance is of course to increase the dose delivered to tumors. But toxicity, as mentioned above, represents a limit that is difficult to overcome. Nevertheless, this approach has already proven its usefulness, as shown by the use of techniques that have ballistic qualities that allow higher doses to the target thanks to more precise conformation capacities and an improved protection of nearby organs at risk. A first step has been taken in this field by the generalization of IGRT with intensity modulation (IMRT and VMAT), which has made it possible to climb a step in terms of the delivered dose by increasing it by approximately 10 to 20% (increased from 55–60 Gy to 66 Gy for example) for the same or even lower toxicities [12].

But other advances based on the physical qualities of radiation are possible.

An additional step consists of matching the ballistic capabilities of the radiotherapy devices and the tumor biology [51]. Thus, the possibility of specifically defining the radioresistance characteristics of tumors, in particular by the presence of hypoxia zones, makes it possible to deliver localized dose increments in hypoxic/radioresistant zones by the dose painting

technique mentioned above. But this technique is supposed to know at each session (therefore each day) where these areas of hypoxia are located in the tumor and to adapt the treatment to them in real time. The means to do this do not yet exist but an approach using a combination of a PET camera and a Linac could be interesting [52].

Finally, approaches based on even more innovative irradiation methods to force tumor radioresistance in a less discriminating way than by the daily imaging of hypoxia or other markers of radioresistance, could come from the use of hadrontherapy. Indeed, hadrontherapy introduces an additional notion of relative biological efficacy that is higher than X-rays in their ability to destroy tumors [53].

Actually, all radiotherapy techniques using ionizing radiation are based on the same mechanisms. Namely, the production of powerful oxidizing radicals by the radiolysis of water in tissues and cells. These radicals are responsible for most of the molecular damages to DNA that are essentially, regarding the types to be considered for cell lethality, complex damages often summarized by the term of DNA double-strand breaks.

Nevertheless, a certain number of distinctions at the nanometric scale can be made between the different types of radiations, particularly in terms of ionization density along the trajectories crossing the tumors. X-rays (photons) produce very diffuse ionizations causing few complex damages relatively distant from each other, producing very diffuse oxidative stress that effectively stimulates the cellular defenses. Thus, as mentioned previously, X-rays can stimulate EMT and reinforce the CSC phenotype and therefore induce their own radioresistance [54].

Conversely, ions such as protons (protontherapy) or heavier ions (hadrontherapy) obtained from carbon, oxygen, or helium atoms will cause very high ionization densities (100 to 1000 times more important than X-rays [55]) bringing a lot of complex damages close to each other in the very interior of the cell nucleus leading to irreversible damages capable of exceeding the radioresistance capacities of the cells. In addition, the grouping of ionizations along the trajectories, less numerous at an equal dose for the ions, considerably reduces the intracellular oxidative stress [54]. Thus, for cells surviving irradiation by ions, the cellular defense reactions elicited by irradiation will be much weaker than for X-rays. These two characteristics: greater physical efficiency and less capacity to stimulate tumor radioresistance, mean that ion therapy may have a greater efficacy on radioresistant tumors compared to X-rays. It is very likely that the very characteristics of tumor stem cells can explain this property and one can imagine that the in-depth analysis of tumors, possibly their greater or lesser richness in CSCs, can also ultimately be a guiding factor towards irradiation by ions rather than by photons.

Thus, faced with the various oncological situations of radioresistance, hadrontherapy represents a hope of progress in terms of the locoregional treatment of conceptually rather simple implementation.

However, the progression of the local control can always be discussed if the tumor evolution remains strongly marked by the metastatic evolution. Nevertheless, it should be kept in mind that local control remains essential for any hope of a cure, and that the primary tumor represents a cellular reservoir capable of producing variants resistant to successive systemic treatments. In addition, advances in systemic treatments and even the synergies between these systemic treatments and radiotherapy, in particular as for the forcing of the immune checkpoints, are approaches that reinforce the interest of locoregional treatment by radiotherapy [56].

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