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REVIEW

Immunotherapy in inoperable stage III non-small cell lung cancer: a review

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Abstract

The leading cause of cancer-related deaths in the United States continues to be lung cancer. Approximately 25–30% of patients are diagnosed with locally advanced non-small cell lung cancer (NSCLC). Concurrent chemoradiation with a platinum-based doublet is the current standard of care for patients with inoperable stage III NSCLC. Unfortunately, only 15–20% of patients treated with definitive chemoradiation are alive at 5 years. Thus, there has been a major unmet need in this area. In this article, we summarize the current status and ongoing clinical trials incorporating immunotherapy into the management of inoperable stage III NSCLC, and we also present our perspective on the future directions.

Keywords: immunotherapy, inoperable NSCLC, stage III NSCLC.

Citation

Jain NA, Otterson GA. Immunotherapy in inoperable stage III non-small cell lung cancer: a review. Drugs in Context 2019; 8: 212578. DOI: 10.7573/dic.212578

Introduction

Lung cancer remains the leading cause of cancer-related death in the United States. Approximately 25–30% of patients are diagnosed with locally advanced non-small cell lung cancer (NSCLC).[1,2] Stage III NSCLC is a heterogeneous disease with three subsets – stage IIIA, IIIB, and IIIC – based on the differences in the extent and localization of disease and extent of adenopathy. Approximately one-third of patients with stage IIIA disease are considered operable (typically with non-bulky and single station ipsilateral mediastinal node involvement), and the standard of care in these patients is preoperative therapy (chemotherapy or chemoradiation) followed by surgical resection. Most patients with stage IIIA/B/C NSCLC, however, are considered inoperable for a multitude of anatomic and sometimes medical reasons. The standard of care for inoperable stage III disease is concurrent chemoradiation with a platinum-based doublet.[3,4] Unfortunately, only 15–20% of these patients are alive and presumably cured 5 years after completion of treatment.[5,6] There is a pressing unmet need for improvements in the management of unresectable local-regional NSCLC.[7–9]

Various strategies to improve the outcomes of patients with stage III NSCLC have been attempted over the last 20–30 years (since the establishment of chemoradiation as the standard of care). This includes increased radiation dose, novel techniques, and the addition of novel cytotoxic or targeted agents to improve local and distant disease control, respectively. Examples of these attempts include a number of randomized studies utilizing induction chemotherapy followed by definitive chemoradiation. For example, the Cancer and Leukaemia Group B (CALGB) performed a study of chemoradiation using weekly carboplatin and paclitaxel with 60 Gy radiation with a randomization of two cycles of 'full dose' paclitaxel and carboplatin or no induction. Although feasible, none of these showed any improvement in overall survival (OS).[10] Similarly, although consolidation chemotherapy (following a definitive course of chemoradiation) was widely used, the Hoosier Oncology Group evaluated the benefit of adding three cycles of consolidative docetaxel following 60 Gy of radiation with concurrent cisplatin and etoposide, and it found no improvement in survival but increased toxicity.[11] The addition of consolidative targeted therapy using 2 years of gefitinib in an unselected patient population (i.e. not selected for the presence of epidermal growth factor receptor [EGFR] mutations) similarly showed no benefit in a Southwest Oncology Group (SWOG) study with worse survival seen in the experimental arm.[12]

The most recent large, randomized study to test dose intensification as well as the incorporation of novel therapies with chemoradiation was RTOG 0617. In this study, the Radiation Therapy Oncology Group (RTOG) conducted a large-scale prospective phase III study (RTOG 0617) to establish the safety and efficacy of increased total radiation dose (60 *versus* 74 Gy)

with concurrent chemotherapy (carboplatin-paclitaxel – including consolidation chemotherapy). A second randomization in this 2 × 2 factorial study included assignment of patients to concurrent treatment with or without cetuximab. The 74 Gy arm had, unfortunately, increased risk of death, with a median survival of 20 months *versus* 29 months in the control (60 Gy) arm. This led to early termination of the study. Multivariate analysis found increased doses to the heart and maximum grade oesophagitis amongst other factors that negatively impacted OS.[13] The addition of cetuximab to either the high-dose or low-dose arm of radiation resulted in increased toxicity, whilst no impact on overall outcomes or survival was noted.

Several trials were conducted to selectively increase the dose to the tumour using a stereotactic boost after conventional radiation therapy. The initial results were promising in terms of feasibility and local control; however, there have been no large scale results yet reported of this strategy.[14]

In this article, we summarize the results of the recently reported PACIFIC trial, an international randomized, double-blinded phase III clinical trial in patients with unresectable stage III NSCLC, which incorporated the addition of durvalumab (*versus* placebo) as consolidation/maintenance therapy following the completion of chemoradiation. We also briefly summarize the ongoing clinical trials incorporating immunotherapy into the management of inoperable stage III NSCLC, and we present our perspective on the future options in this setting.

Rationale for immunotherapy

Several clinical trials have established the role of immune checkpoint inhibitors in metastatic NSCLC after progression on at least one prior line of treatment and subsequently as first-line treatment (either alone or in combination with cytotoxic chemotherapy).[15–17] Given the improvement over chemotherapy alone seen in these studies, the simple clinical question evaluating the role of immunotherapy in locally advanced inoperable stage III NSCLC, with the potential to build on the current established regimen of chemoradiation. In addition, preclinical evidence had suggested the possibility of an additive or synergistic impact of combining PD1/PDL1 blockade with radiotherapy.[12,18]

Finally, an abscopal effect for combining radiation and immunotherapy has been advanced. The abscopal effect has been frequently discussed, but not well understood. It is defined as the regression of the distant metastasis when the primary tumour is radiated.[19] Radiation is hypothesized to increase tumour immunogenicity by releasing circulating tumour antigens. This in turn mediates an augmented immune response against distant metastatic lesions.[20] T-cell priming in draining lymphoid tissues is drastically increased by ablative radiation therapy. The primary tumour or distant metastases are subsequently regressed in a CD8+ T-cell-dependent fashion.[21] Immunotherapy amplifies these RT-related immune responses. Clinical evidence supporting the complementary roles for Cytotoxic T-lymphocyte-associated protein (CTLA-4) and PD-1 antagonists followed by radiation provides the abscopal effect.[22–24] Postow and colleagues described a case of metastatic melanoma with progression whilst on ipilimumab, who had a systemic response to localized radiotherapy with disease regression at distant sites. The 19-month interval between starting ipilimumab and disease response, with radiotherapy administration in the interim was thought to be an abscopal effect.[25]

Consolidation immunotherapy

The role of consolidation immunotherapy in inoperable stage III NSCLC was established by the phase 3 PACIFIC study, which enrolled patients following completion of chemoradiation. The study required patients to have received definitive radiation (between 54 and 66 Gy) with appropriate lung dose constraints along with two or more cycles of platinum-based chemotherapy. After completion of chemoradiation (within 14–42 days), patients were randomly assigned to durvalumab (a highly selective IgG1 monoclonal antibody that blocks PDL1 binding to PD-1 and CD80) or placebo in a 2:1 ratio. There were 713 patients randomized, and 709 patients received either durvalumab (dose of 10 mg/kg) or placebo every 2 weeks for up to 1 year. The trial met its primary endpoint of improved progression-free survival (PFS) with durvalumab (16.8 months), which was much longer compared with placebo (5.6 months). The corresponding hazard ratio for disease progression or death was 0.52 (95% confidence interval of 0.42–0.65). The secondary endpoints also favoured durvalumab. Durvalumab had a higher response rate (28.4 *versus* 16.0%; $p<0.001$) as well as longer median duration of response at 18 months (72.8 *versus* 46.8%) compared to placebo. Durvalumab had a longer median time to death or distant metastasis (23.2 *versus* 14.6 months; $p<0.001$). Toxicity was carefully monitored, as it had been a concern, especially the potential for overlapping pulmonary toxicity. Pneumonitis (any grade) occurred in 33.9% of patients in durvalumab group compared with 24.8% in the placebo group. Grade III or pneumonitis was observed in 3.4 and 2.6%, respectively.[26] Other described pulmonary toxicity events including pneumonia and cough were numerically higher in the durvalumab arm; however, dyspnea was somewhat more common in the placebo arm.

After additional follow up, the study also recently met its second primary endpoint of OS at a median follow up of 25.2 months. Moreover, 24-month OS in the durvalumab (66.3%) arm was significantly higher compared with placebo (55.6%) ($p=0.0025$).[27] Similar PFS was reported in the updated analysis (17.2 months in the durvalumab group compared with 5.6 months in the placebo group). Patients treated with durvalumab had a median time-to-death or distant metastasis of 28.3 months compared with 16.2 months for those treated in the placebo group.[27] In an analysis of OS for prespecified subgroups, there was a trend to improved survival in patients who had received prior chemotherapy with cisplatin compared with carboplatin. Similarly, there was a trend towards improved

survival in patients with earlier randomization to durvalumab post radiation (<14 days) compared with later (>14 days). Similarly, in the *post hoc* exploratory subgroup analysis based on PD-L1 expression (≥25 *versus* <25%), improved PFS as well as OS was seen in each of the PD-L1 subgroups, though the difference was borderline for the low expression group.

Regulatory authorities requested additional *post hoc* subgroup analysis based on PD-L1 expression to include patients with ≥1%, ≥25%, 1–24%, and <1%. In this analysis, unstratified hazard ratios for disease progression favoured durvalumab in all groups (though the hazard ratio for the <1% subgroup of patients was 0.73 with confidence interval crossing unity), and the unstratified hazard ratio for death was 1.36 (0.79–2.24) in this group. It has been noted that tumour tissue collection was not mandated in the inclusion criteria. The PD-L1 expression status was available for a subset of the intention-to-treat (ITT) population (451 out of 713, 63%). Retrospective testing for tumour PD-L1 expression was conducted for the remaining subjects using archival tumour tissue. There are significant limitations to the *post hoc* subgroup analysis, including no prespecified statistical adjustment, small sample size of the subgroups, and incomplete tissue samples in the ITT population. As such, one might consider this *post hoc* analysis of the hazard ratios using the 1% cut-off as hypothesis generating.[27] In the United States, Food and Drug Administration has approved durvalumab as a consolidation therapy after chemoradiation in unresectable stage III NSCLC, irrespective of PD-L1 expression. However, the European Medicines Agency has limited its use in unresectable stage III NSCLC with PD-L1 expression >1%.[28,29]

Fortunately, the toxicity seen with the strategy of consolidation/maintenance checkpoint inhibitors (specifically durvalumab in the PACIFIC trial) has been acceptable. As noted earlier, pneumonitis in particular was of concern given the known toxicities of radiation and PD1/PDL1 antibodies when administered separately. Prospective clinical trials are needed for careful clinical evaluation of the combination of chemoradiotherapy with immunotherapy.

Additional consolidation/maintenance immunotherapy trials with alternative checkpoint inhibitors are ongoing, including PD1 antibodies as well as the combination of PD1 and CTLA4 antibodies. Table 1 summarizes the ongoing clinical trials registered on clinicaltrials.gov as of 1 September 2018, using consolidation immunotherapy after definitive chemoradiation.

Concurrent immunotherapy

The safety (particularly pneumonitis) of a sequential chemoradiation followed by immunotherapy seen in the PACIFIC

Table 1. Ongoing clinical trials of adjuvant immunotherapy in inoperable NSCLC.

NCI identifier	Phase	Number of patients	Immunotherapy	Primary endpoint	Projected completion date	Recruiting status
NCT03285321	II	108	Ipilumab, Nivolumab	PFS	30 Sep 22	Recruiting
NCT02768558	III	13	Nivolumab	OS, PFS	Oct 24	Active, not yet recruiting
NCT02525757	II	52	Atezolizumab	Time to toxicity	Jan 21	Active, not yet recruiting
NCT03379441	II	126	Pembrolizumab	OS	Jan 23	Not yet recruiting

Table 2. Ongoing clinical trials of concurrent immunotherapy in inoperable NSCLC.

NCI identifier	Phase	Number of patients	Immunotherapy	Primary endpoint	Projected completion date	Recruiting status
NCT02621398	I	30	Pembrolizumab	Maximum tolerated dose and dose limiting toxicity	Oct 19	Recruiting
NCT02343952	II	93	Pembrolizumab	Time to death or distant metastasis	Jun 19	Active, not yet recruiting
NCT02125461	III	713	Durvalumab	OS, PFS	9 Jul 19	Active, not yet recruiting
NCT02434081	II	94	Nivolumab	Grade ≥3 pneumonitis from the end of radiotherapy	Aug 20	Active, not yet recruiting

study has given greater comfort in designing trials of concurrent chemoimmunoradiotherapy. Table 2 summarizes some of these ongoing clinical trials registered on clinicaltrials.gov as of 1 September 2018.

Conclusion

The role of immunotherapy is now well established in metastatic NSCLC, as well as in locally advanced inoperable stage III NSCLC in the consolidation setting (PACIFIC trial). Clinical trials evaluating other immunotherapeutic agents such as pembrolizumab, nivolumab, ipilumumab, and atezolizumab are currently undergoing. Several questions including the timing of immunotherapy (consolidation *versus* concurrent with definitive chemoradiation), selection of patients who will benefit most from immunotherapy and importantly biomarkers (PDL1 or others) still remain unanswered. As these ongoing clinical trials mature, they may provide further insight into the management of inoperable stage III NSCLC using immunotherapy.

Contributions: Both the authors did the literature search, wrote the manuscript, and critically edited it. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Disclosure and potential conflicts of interest: Dr Otterson reports grants from Genentech, BMS, Merck, Novartis, Pfizer, Celgene, and Astra Zeneca, and consultant fees from Pfizer, Novartis, Takeda, Amgen, and Novocure, outside the submitted work. Dr Jain declares no conflicts of interest. The International Committee of Medical Journal Editors (ICMJE) Potential Conflicts of Interests form for the authors is available for download at http://www.drugsincontext.com/wp-content/uploads/2019/05/dic.212578-COI.pdf

Acknowledgements: None.

Funding declaration: There was no funding associated with the preparation of this article.

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Article URL: https://drugsincontext.com/immunotherapy-in-inoperable-stage-iii-non-small-cell-lung-cancer:-a-review

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Provenance: invited; externally peer reviewed.

Submitted: 9 January 2019; **Peer review comments to author:** 14 February 2019; **Revised manuscript received:** 17 May 2019; **Accepted:** 20 May 2019; **Publication date:** 17 June 2019.

Drugs in Context is published by BioExcel Publishing Ltd. Registered office: Plaza Building, Lee High Road, London, England, SE13 5PT.

BioExcel Publishing Limited is registered in England Number 10038393. VAT GB 252 7720 07.

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