Hyperprogression after Immunotherapy: Nivolumab. Analysis of Imaging Findings Associated with Hyperprogression and Tumor Growth Kinetics

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Abstract

Introduction The increased use of new checkpoint inhibitors in cancer therapy has led to the discovery of new unconventional responses, like pseudoprogression and hyperprogression disease (HPD). The study documents imaging findings of HPD and analyzes the growth kinetics in advanced metastatic cancers patients treated with immunotherapy.

Methods We retrospectively reviewed patients treated with anti-PD-1 (anti-progressive disease-1) antibody therapy (nivolumab) between January 2017 and December 2017 at our institute. The patients who exhibited early and rapid progression rates after initiation of immunotherapy were further analyzed for tumor growth kinetics (TGKs) and imaging findings. All prebaseline, baseline, and post nivolumab imaging were retrospectively reviewed to assess the TGKs, time to treatment failure (TTF), and rate of progression according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.

Results Four patients with HPD had peculiar imaging appearance of unilateral circumferential nodular pleural thickening along with conglomerate pleural masses and effusions. Both primary and secondary sites progressed along with the appearance of new lesions in all these patients. The mean progression-free survival (PFS) was 32 days using Kaplan Meier analysis.

Conclusion The unique and recurring imaging pattern of disease progression in patients with HPD as reported in our case series in addition to TGK ratio, and TTF may prove to be of additional help in early identification of this unique and ghastly outcome.

Keywords
► advanced metastatic lung cancer
► hyperprogression
► immunotherapy
► tumor growth kinetics

Background
Nivolumab, an anti-PD-1 (anti-progressive disease-1) checkpoint inhibitor, has demonstrated efficacy in patients with advanced or metastatic non-small cell lung cancer (NSCLC), melanoma, small cell lung cancer, renal cell cancer, urothelial and head and neck cancers after failure to standard chemotherapeutic agents. Unlike treatment response after

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Hyperprogression after Immunotherapy

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Definition of Hyperprogression

Champiat et al. described HPD as a Response Evaluation Criteria in Solid Tumors (RECIST) progression at the first evaluation and a twofold or greater increase in tumor growth rate from baseline (before treatment with immunotherapy). Similarly, Saâda Bouzid et al. defined hyperprogression as tumor growth kinetics (TGKs) ratio equal to or greater than 2 in patients with head and neck cancer on immunotherapy. Kato et al used a three-point definition of hyperprogression:

1. Time-to-treatment failure (TTF) of less than 2 months.
2. Greater than 50% increase in tumor burden compared with preimmunotherapy imaging.
3. Greater than or equal to a twofold increase in progression pace.

Methods

This is a retrospective study and was approved by the local ethics committee of Rajiv Gandhi Cancer Institute & Research Centre. Owing to the retrospective nature of the study, informed consent from patients was not required. We describe four patients with stage IV lung and renal cancer who received nivolumab immunotherapy and showed hyperprogression (Table 1). All but one patient was advanced metastatic lung cancer who progressed on previous multiple lines of chemotherapy.

Patients treated with monotherapy by anti-PD-1/PD-L1 antibodies, i.e., nivolumab between January 2016 and December 2017, were examined. Amongst them, one who exhibited early and rapid progression rates after the initiation of nivolumab were studied and analyzed. All the CT scans were independently reviewed by two senior radiologists. Patients with prebaseline CT scans were included to assess TGR before starting nivolumab. All prebaseline, baseline, and post nivolumab imaging were retrospectively reviewed to assess the TGKs, TTF, and increase in progression pace according to RECIST 1.1.

The following data were also recorded: age, gender, PD-L1 analysis, patterns of hyperprogression, date of start of nivolumab, and date of last follow-up or adverse event such as death.

\[ T_{PRE}, T_0, T_{POST} \] stand for the time of prebaseline, baseline, and first imaging, respectively. \[ S_{PRE}, S_0, S_{POST} \] stand for the sum of the largest diameter of target lesions at prebaseline, baseline, and first imaging, respectively. TGK PRE was defined as the difference of the sum of the largest diameters of the target lesions (according to RECIST) per unit of time between prebaseline and baseline imaging: \[ (S_0 - S_{PRE})/(T_0 - T_{PRE}) \]. Similarly, TGK POST was defined as: \[ (S_{POST} - S_0)/(T_{POST} - T_0) \].

The TGK ratio (TGK R) was defined as the ratio of TGK POST to TGK PRE. TGK R > 1 indicated tumor growth acceleration, whereas 0 < TGK R < 1 and TGK R < 0 indicate tumor deceleration and tumor shrinkage, respectively. Hyperprogression was defined as TGK R ≥ 2.

Statistical Analysis

Descriptive statistics is presented with line graphs. TGK R was calculated using the formula given in the assessment section. Kaplan Meier analysis was performed for progression-free survival (PFS). Median PFS with a 95% confidence interval was reported.

Results

There were four patients with advanced metastatic lung/renal cancer treated with monotherapy by anti-PD-1/PD-L1 antibodies in this case-series. Table 1 shows the demographic and clinical details of these four patients. Fig. 1 represents diameter growth according to RECIST 1.1 criteria. The sum of the diameter shows an exponential increase after treatment with nivolumab (Figs. 1 and 2).

Three out of four (75%) patients showed accelerated growth measured through TGKs (Cases 1, 2 and 4 TGK > 2) (Figs. 3-6). Case 3 also developed rapid worsening of symptoms after two cycles of nivolumab monotherapy. The X-ray chest showed marked increase in air space opacities and pleural effusion. The patient also developed anterior wall myocardial infarction, and hence cross-sectional imaging could not be performed at the time of onset of symptoms due to his poor general condition. Hence TGK recorded is less than 2 for case 3. However, the increase in tumor burden was > 50% as compared with prebaseline imaging, and TTF was less than 2 months.

Median progression-free (95% CI) survival was 32 (21.2–42.8) days (Fig. 3).

Contrast-enhanced computed tomography chest findings were notably similar in all of them. There was a development of unilateral circumferential pleural nodularity with conglomerate pleural masses and associated pleural effusion. The laterality corresponded to the side of primary baseline disease.

Discussion

In our series, all but one patient experienced hyperprogression as defined by TGK R > 2 after anti-PD-1/PD-L1 therapy. We
Table 1  Clinical characteristics of patients

<table>
<thead>
<tr>
<th></th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>62 y</td>
<td>56 y</td>
<td>46 y</td>
<td>62 y</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td>Male</td>
<td>Male</td>
<td>Male</td>
<td>Male</td>
</tr>
<tr>
<td><strong>Primary diagnosis</strong></td>
<td>mRCC</td>
<td>mNSCLC</td>
<td>mNSCLC</td>
<td>mNSCLC</td>
</tr>
<tr>
<td><strong>Date of detection</strong></td>
<td>May 2016</td>
<td>July 2016</td>
<td>April 2013</td>
<td>July 2017</td>
</tr>
<tr>
<td><strong>EGFR/ALK mutation status</strong></td>
<td>Not done</td>
<td>Negative</td>
<td>EGFR mutant</td>
<td>Negative</td>
</tr>
<tr>
<td><strong>Anti PD-1, PD-L1 status</strong></td>
<td>Not done</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td><strong>Treatment history</strong></td>
<td>Surgery for both primary and metastatic site followed by CT/RT till November 16. PD in May 17, Palliative CT.</td>
<td>CT/RT till November 16. PD in May 17, Palliative CT.</td>
<td>Multiple lines of CT till June 2015-PD, Gefitinib/</td>
<td>Three cycles of chemotherapy. PD</td>
</tr>
<tr>
<td></td>
<td>Sutent</td>
<td>Six cycles till September 17. PD in October 2017.</td>
<td>Erlotinib till September 16-PD.</td>
<td></td>
</tr>
<tr>
<td><strong>Duration of treatment before progression</strong></td>
<td>6 mo</td>
<td>1 y 3 mo</td>
<td>3 y 5 mo</td>
<td>3 mo</td>
</tr>
<tr>
<td><strong>CT findings (Baseline)</strong></td>
<td>Bilateral lung lesions, mediastinal lymphadenopathy, bilateral pleural effusions, pericardial effusion, bone lesions.</td>
<td>Left hilar mass, right lung nodules, moderate left pleural effusion.</td>
<td>Left lung upper lobe mass, bilateral lung nodules, mediastinal, and left lower cervical lymph nodes.</td>
<td>Right lung mass with mediastinal lymph nodes and left adrenal metastasis.</td>
</tr>
<tr>
<td><strong>Date of start of nivolumab</strong></td>
<td>January 18, 2017</td>
<td>October 12, 2017</td>
<td>September 24, 2016</td>
<td>October 12, 2017</td>
</tr>
<tr>
<td><strong>duration of immunotherapy</strong></td>
<td>Two cycles</td>
<td>One cycle</td>
<td>Four cycles</td>
<td>One cycle</td>
</tr>
<tr>
<td><strong>CT findings (Post nivolumab).</strong></td>
<td>&gt;twofold increase in the size of lung lesions, new circumferential left-sided nodular pleural thickening with a 150% increase in the size of mediastinal lymph nodes.</td>
<td>Progressive left lung mass with new left-sided nodular pleural thickening and minimal right pleural effusion.</td>
<td>Progressive left lung mass and bilateral lung nodules, progressive mediastinal lymph nodes, new circumferential left pleural deposits, new brain, liver, adrenal, and bone lesions.</td>
<td>Progressive right hilar lung mass, new bilateral pleural effusion, diffuse nodular circumferential right pleural thickening and nodular deposits, progressive mediastinal lymph nodes.</td>
</tr>
<tr>
<td><strong>Last follow-up</strong></td>
<td>LFU</td>
<td>LFU</td>
<td>LFU</td>
<td>Died of cardiac arrest in November 2017</td>
</tr>
</tbody>
</table>

Abbreviations: ALK, anaplastic lymphoma kinase; CT, computed tomography; EGFR, epidermal growth factor receptor; LFU, lost to follow-up; NSCLC, non-small cell lung cancer; PD, progressive disease.

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Fig. 1 Diameter growth before and after nivolumab.

Fig. 2 TGKs before and after. TGK, tumor growth kinetics.
could not perform CT chest imaging of one patient when he
developed worsening of symptoms leading to discontinua-
tion of treatment. This led to an increase in the time duration
between two assessment scans, i.e., $T_{post} - T_0$ and a decrease
in TGK, to less than 2. However, TTF was <2 months in all
four patients in accord with the definition given by Kato et
al. Also, there was >50% increase in tumor burden at the time
of next imaging compared with preimmunotherapy imaging
fulfilling one of the criteria of HPD. But it is important to
note here that the patient was not under any kind of anti-
cancer treatment during this period making this observation
suboptimal.

Hyperprogression was associated with poor prognosis in
our study, in accord with other published reports. HPD was
associated with short PFS (32 days) in our series. We could
not calculate overall survival as three out of four patients lost
to follow-up.

Kato et al. investigated potential genomic markers associ-
ated with hyperprogression after immunotherapy. They
reported TTF <2 months in six of 155 patients and TGK >2 and an increase in tumor burden of >50% in four out
155 patients. They also suggested MDM 2/MDM 4 and epi-
dermal growth factor receptor (EGFR) alterations correlated
with TTF <2 months. We could not establish any correlation
between EGFR aberrations in our case series and hyperpro-
gressors. Two out of four patients were EGFR/anaplastic lym-
phoma kinase (ALK)-negative. One patient was EGFR mutant
and EGFR/ALK analysis was not performed in the patient of
metastatic renal cell cancer.

Champiat et al. demonstrated that 9% of patients (12/131)
showed a >twofold increase in tumor growth in their study.
They observed that HPD was associated with older age and
with worse overall survival. They observed no correlation
between hyperprogression and baseline tumor burden and the
number of previous lines of chemotherapies. Twenty-seven
percent of their patients underwent PDL-1 testing and they
did not find any difference of PD-L1 status between HPD and
other patients.

All our patients underwent anti-PD-L1 testing and were
negative. The role of PD-L1 expression/amplification is known
in predicting response to immunotherapy but no correlation
has been established between HPD and anti-PD-L1 status
till date.

We also describe the pattern of hyperprogression in our
case series, which has not been described in any previous
study. The imaging pattern observed was independent of pri-
mary tumor type and we recorded similar findings in all the
four cases such as unilateral diffuse pleural nodularity with
loss of ipsilateral hemithoracic volume. The pleural nodular
thickening was circumferential and extensive forming con-
glomerate large-sized pleural masses. None of these patients
had pleural disease at the beginning of treatment. Unilateral
circumferential nodular pleural thickening was a key finding
and was seen on the side of primary lung mass. This finding
was unique with immunotherapy as these patients also pre-
viously received multiple lines of chemotherapy and showed
no such imaging features. These patients also developed either
new or increase in pleural effusion after immunotherapy. All
patients showed progression at both primary and secondary sites. The imaging findings correlated well with the severity of patient’s symptoms.

Our series is unique as no previous study has described these imaging findings.

Immunotherapy can also lead to unconventional responses such as pseudoprogression. Pseudoprogression is radiological progression followed by a response on subsequent imaging on sustained immunotherapy. It is important to differentiate between the two as hyperprogression calls for immediate discontinuation of treatment, whereas treatment is continued for pseudoprogression exhibiting clinical response. As mentioned earlier, hyperprogression can be measured by assessing TGK<sub>r</sub>, tumor burden, and TTF. The chief factor before discontinuing treatment is clinical status. The HPD patients show significant clinical deterioration, whereas pseudoprogression is considered when a patient is showing a clinical benefit.

Our study has several limitations. Its biggest limitation is the small size. The second limitation is that we used RECIST 1.1 criteria which are now replaced by iRECIST criteria for response evaluation after immunotherapy. These criteria are different from RECIST1.1 in that radiologically progressive disease needs to be confirmed by a follow-up examination in case of clinical response. All our patients showed severe clinical worsening, and hence no confirmatory scans were performed.

Also, in contrast to RECIST 1.1, the summed diameters of new lesions appearing on follow-up examinations are recorded separately (maximum two per organ, five overall) for iRECIST and not included in the sum of the tumor burden at baseline or time of nadir. Using RECIST 1.1 we did not record the diameter of new lesions that appeared at time point T<sub>0</sub> and hence could not assess their contribution to tumor burden at time point T<sub>post</sub>.

However, it is also noteworthy to mention that most of the definitions of HPD suggested by various authors used RECIST 1.1 criteria. Presently, iRECIST criteria do not have provisions to recognize hyperprogression or differentiate hyperprogression from pseudoprogression. In view of this limitation, the early identification of HPD becomes even more important as it warrants cessation of treatment in contrast to immune unconfirmed progressive disease, which ensues treatment beyond progression.

**Conclusion**

The unique and recurring imaging pattern of disease progression in patients with HPD as reported in our case series in addition to TGK<sub>r</sub> and TTF may prove to be of additional help in early identification of this unique and mostly lethal treatment outcome. The radiologist may have a key role in alerting medical oncologists to potential risks of these new treatments. Further large patient cohort studies are needed to explore the imaging patterns of hyperprogression and to recognize genomic alterations and imaging predictors associated with HPD.

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None.

**Conflict of Interest**

None declared.

**References**