Cumulative pemetrexed dose increases risk of nephrotoxicity

* A retrospective cohort study

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ICPAD – November 21st – 22nd
Incidence

1. Lung
   - 11.6% of all new cases
   - 2.094 million

2. Breast
   - 11.6% of all new cases
   - 2.089 million

3. Colorectal
   - 10.2% of all new cases
   - 1.8 million

4. Prostate
   - 7.1% of all new cases
   - 1.3 million

5. Stomach
   - 5.7% of all new cases
   - 1.3 million

For both sexes, all cancers for all ages, worldwide in 2018

Data source: GLOBOCAN 2018
Available at Global Cancer Observatory [https://gco.iarc.fr]
© International Agency for Research on Cancer 2018

Mortality

1. Lung
   - 18.4% of all cancer deaths
   - 1.4 million

2. Colorectal
   - 9.2% of all cancer deaths
   - 881 000

3. Stomach
   - 8.2% of all cancer deaths
   - 783 000

4. Liver
   - 8.2% of all cancer deaths
   - 782 000

5. Breast
   - 6.6% of all cancer deaths
   - 627 000

For both sexes, all cancers for all ages, worldwide in 2018
Treatment of NSCLC and mesothelioma

• Chemotherapy
  • Pemetrexed + platinum induction
  • Pemetrexed maintenance

• Chemo-immunotherapy
  • Pembrolizumab + pemetrexed + platinum induction
  • Pembrolizumab + pemetrexed maintenance
Pemetrexed – pharmacotherapeutic cornerstone

• Renal elimination – up to 90% unchanged within 24 hours
• Correlation creatinine clearance – exposure – neutropenia
• Label: contraindicated CrCl <45mL/min.

! Loss of renal function can be a treatment limiting complication
Aim of this study

• To investigate the incidence of nephrotoxicity and related treatment consequences during pemetrexed-based treatment

• To identify risk factors for a decline in renal function during pemetrexed-based treatment
Outcome measures and methods

• Primary outcome
  • ≥25% reduction in eGFR
  • Treatment discontinuation due to nephrotoxicity

• Secondary outcome
  • Risk factors for nephrotoxicity

• Exploratory:
  • Neutropenic events cases vs non-cases

> Descriptive statistics
> Descriptive statistics
> Logistic regression
> Descriptive statistics/Fisher’s exact
Methods

• Retrospective patient file study Jeroen Bosch Hospital
  • 01-Jan-2014 to 01-Feb-2019
  • At least 1 cycle of pemetrexed

• Patient demographics
• Information regarding treatment
• Serum creatinine → CKD-EPI

Demographics for risk factor analysis

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Details</th>
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</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
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<tr>
<td>Age</td>
<td></td>
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<tr>
<td>Baseline eGFR</td>
<td></td>
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<tr>
<td>BMI</td>
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<tr>
<td>Diagnosis/lung cancer type</td>
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<tr>
<td>Pre-treatment</td>
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<tr>
<td>Smoking status</td>
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<tr>
<td>(no. of) comorbidities*</td>
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<tr>
<td>(no. of) comedication*</td>
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<tr>
<td>Concomitant induction therapy types</td>
<td></td>
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<tr>
<td>Total no. of cycles</td>
<td></td>
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</tbody>
</table>

*predefined comorbidities and comediations that may affect renal function
Results – demographics

- 54% male
- Median age 65 yrs
- 69% stage IV NSCLC
- 73% first line treatment
- Median no of cycles: 4 (range: 1-103)
- 88% past or current smoker

N=386
N=359
N=27 missing data
Results – primary outcome

21% of patients ≥25% reduction in eGFR

8.1% of patients discontinues treatment due to nephrotoxicity

1/3rd with hematotoxicity
Results – secondary outcome

≥ 10 cycli adjusted OR 5.66 (1.73-18.54), p<0.001
Results – exploratory

• More neutropenic events in group ≥25% reduction in eGFR

Cases: 35.1% of patients ≥1 neutropenic event

Non-cases: 13.6% of patients ≥1 neutropenic event
Discussion

• Cumulative effect or physiological decline over time

• Chemo-immuno SoC ➔ nephrotoxic potential checkpoint inhibitors

• Mechanism of toxicity

• Use of serum creatinine / CKD-EPI
Conclusion

• High incidence of clinically relevant decline in renal function \( \rightarrow \) treatment limiting

• Risk of renal impairment increases with longer treatment duration and seems associated with increased risk on hematotoxicity

• Combined immunochemotherapy: longer survival and thus treatment duration
Thanks

• Heidi vd Bruinhorst – Pharmacy student UU
• Rabdoudumc
  • Prof. Dr. L. Hilbrands – dept. Nephrology
  • Prof. Dr. M.M. van den Heuvel – dept. Pulmonology
  • Dr. R. ter Heine – Clinical Pharmacy
  • Prof. Dr. D.M. Burger – Clinical Pharmacy
• Jeroen Bosch Ziekenhuis
  • Dr. H.J. Derijks – Clinical Pharmacy
  • Dr. B. Biesma – dept. Pulmonology
• René Boosman – PhD colleague NKI-AvL