Melanoma Research and Therapy Special Interest Group meeting

21 September 2023

Background

This meeting of the Melanoma Research and Therapy Special Interest Group was held on Thursday 21 September 2023 in conjunction with the New Zealand Society of Oncology Conference. Topics were:

- Adjuvant and neo-adjuvant therapy and contemporary melanoma surgery
- Real-world outcomes of immunotherapy for melanoma brain metastases in New Zealand

Chaired by Dr Jody Jordan (Medical Oncologist, Hawke's Bay) and Dr Annie Wong (Medical Oncologist, Capital, Coast and Hutt Valley), the meeting was attended by 21 health professionals.

Topic 1: Adjuvant and neo-adjuvant therapy and contemporary melanoma surgery

Presentation from Associate Professor Alexander van Akkooi, Surgical Oncologist and Associate Professor of Melanoma and Surgical Oncology, Melanoma Institute Australia, the University of Sydney and the Royal Prince Alfred Hospital

Presentation summary

- Surgery has been and still is the cornerstone treatment for early-stage (stage I-III) melanoma. The extent of surgery has been and will continue to be re-defined in upcoming years.
- A study by *Gershenwald et al*. showed that despite curative intent surgery, 12-76% of stage III patients still died due to metastatic melanoma. This is due to unidentified micro-metastatic disease at the time of surgery that becomes apparent in due course.
- Adjuvant treatment is a 'preventive' treatment to eliminate micro-metastases. Where there is no micro-metastasis, adjuvant therapy is overtreatment.
- Adjuvant therapy in stage III melanoma consistently shows significant and meaningful improvement in recurrence-free survival, however data does not yet show how this translates into overall survival.
- There are many benefits to neoadjuvant therapy – a stronger and broader anti-tumour immune response, reduced tumour burden which facilitates easier surgical excision, and a potential decreased need for extensive lymphadenectomies which have significant morbidity compared to ILN. These findings have been backed by preclinical models and neoadjuvant trials. However, drug-related toxicity remains an issue.
    - *Menzies et al* demonstrated that a pathologic response after neoadjuvant checkpoint inhibition is associated with prolonged relapse-free survival in stage III melanoma.
    - *SWOG-1801* proposed a simple design whereby the same drug is given, but only the order of the drug is changed. Results showed a huge difference in event-free survival (neoadjuvant 72%, adjuvant 49% at 24 months).
    - The *PRADO* study confirmed the high pathological response rate of *OpACIN-neo* and that total lymph node dissection could be omitted in a substantial subset of patients. *PRADO* was seen as 'proof of concept' but is too small to change practice definitively.

- *OpaCIN-neo v PRADO* showed total lymph node dissection omission does not affect survival outcomes in patients with a major pathologic response.

Conclusions

- Adjuvant Systemic Therapy = a standard of care for stage III melanoma
  - BRAF mutant: dabrafenib & trametinib OR nivolumab OR pembrolizumab
  - BRAF wildtype: nivolumab OR pembrolizumab
- Neo-Adjuvant Systemic Therapy is exciting and might soon become a novel standard of care
- The extent of surgery for stage III is still being defined.
- Total lymph node dissection is still considered routine after neoadjuvant treatment - more data is needed to introduce ILN as routine.

Questions and discussion

- **Why are we seeing such high levels of toxicity in stage III patients treated with neoadjuvant therapy?**
  The host immune system is more inhibited in stage IV patients, less so in stage III. The immune system can therefore be kickstarted easier in stage III patients, but it does also lead to more adverse events as a result.

- **What proportion of the melanoma burden will neoadjuvant address?**
  Not sure. The uptake of Sentinel Lymph Node Biopsy is consistent (about 50% in Australia), and the same trend is seen across the globe.

- Neoadjuvant therapy might be useful in New Zealand where resourcing is an issue, as it only requires two courses of neoadjuvant therapy plus surgery. Brazil has started using this approach due to resourcing issues.

Topic 2: Real-world outcomes of immunotherapy for melanoma brain metastases in New Zealand

Presentation from Niamh Walsh, Research Student (MB ChB), University of Otago Wellington

Presentation summary

- This project assessed treatment outcomes in a real-world population of patients with brain metastases, on steroids, and with poor performance status. This population would typically be excluded from clinical trials.
- Across seven NZ cancer centres, data was collected on patients treated with immunotherapy between 1 September 2016 and 1 September 2020 who were diagnosed brain metastases before commencing treatment.
- 144 patients met the criteria and had been treated with at least one dose of immune checkpoint inhibitors for brain metastases. Most patients (93%) received anti-PD1 monotherapy.
- Almost a quarter of patients had an ECOG of 2 or higher, 56% presented with brain metastases as the first symptom of metastatic disease, and 33% had corticosteroids. Comorbidities of three or more were reported in 53% of patients.
- Intracranial response was seen in 36%, and median iPFS was 9 months. Six and 12-month-iPFS rates were 55% and 45% respectively.
- Median overall survival was 15 months (65% at six months, 53% at 12 months), and a third of patients were alive at 2 years. This was higher than expected.
- Steroid use amongst patients was reported to have a lower median survival rate compared to patients who did not use steroids at the time of starting treatment for symptom control. This is consistent with the literature (5 months vs 20 months). However, disease control was still able to be achieved in this cohort.

- Patients with symptomatic brain metastases had a shorter median survival than patients with asymptomatic metastases: 12 vs 17 months.
- The toxicity of immune checkpoint inhibitors was 28% and 15% for grade 1-2 and 3-4 events respectively. Of the patients who are still alive at 2 years, 77% of patients were symptomatic at last follow up.

Conclusions:

- Despite this population having a poorer prognosis due to frailness, neurological symptoms and greater disease affliction, immune checkpoint inhibitors are an effective treatment for metastatic melanoma patients with brain metastases.

Questions and discussion

- **What was the dosing for patients on steroids?**
  15% less than 4 mg, 81% greater than 4mg. This would be an exclusion criteria for clinical trials.

- **Did you include patients where immunotherapy was planned but not delivered?**
  There were many patients who died before receiving treatment so it was decided to include only those who had received one dose. Some patients died after less than 4 doses.

- **Why does this real-world data look better than trial data?**
  Don't know - were surprised by the results. Perhaps, patients had received treatment so were already 'hardier' and one-third had other disease treatments**.**

- **Do we need to reduce steroid use before starting immunotherapy?**
  Several oncologists in attendance said they were agnostic to steroid use.

- We should not have performance status criteria for special authority as this data demonstrates response (unless there is a safety risk). But we need to be good stewards of resource as well.

- This study demonstrates that we can undertake research studies across the country.

Acknowledgements

MelNet would like to thank the presenters and all those who took the time to attend this meeting.

Next meeting

- The group agreed to meet again in approximately six months.