May 2nd, 12:00 AM

Neoadjuvant versus Adjuvant Therapy for Stage IIIB-IIID Melanoma

Bhumik Patel
Rowan University

Sangnya Upadhyaya

ROWAN - VIRTUA
School of Osteopathic Medicine

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Bhumik Patel, OMS-III, Sangnya Upadhyaya, PharmD

References

Background

- **Evolving Treatment Landscape**: With advancements in our understanding of melanoma biology and the emergence of novel therapies, the treatment landscape for advanced stages is dynamically evolving, necessitating a comprehensive review to guide clinicians in adopting evidence-based and patient-centric approaches.[1]
- **Therapeutic Dilemma**: A debate between neoadjuvant and adjuvant therapy to optimize melanoma treatment outcomes and improve long-term survival rates.

Significance

- **Treatment Optimization**: Provide evidence-based insights to optimize treatment strategies for patients with advanced melanoma, specifically in stages IIIB-IIIC, contributing to more effective and personalized therapeutic approaches.
- **Informed Decision-Making**: Study outcomes will empower both clinicians and patients by offering a deeper understanding of the comparative effectiveness of neoadjuvant and adjuvant therapies, facilitating informed decision-making in the complex landscape of melanoma treatment.
- **Advancements in Melanoma Care**: Potential to catalyze advancements in the field of melanoma care, influencing clinical practices and contributing to the ongoing efforts to enhance outcomes and quality of life for individuals facing advanced melanoma.

Methods

Literature Search:

- PubMed, ASCO, and JAMA Oncology.
- Search period: July 1, 2023 - December 31, 2023

Study Selection:

- Inclusion criteria: melanoma stages IIIB-IIID, use of neoadjuvant therapy in adults.
- Exclusion criteria: studies that did not meet specified inclusion criteria or lacked relevant data on neoadjuvant and adjuvant therapies in stages IIIB-IIID melanoma or did not substantially specify the level disease in its participants.

Table 1. Literature search queries

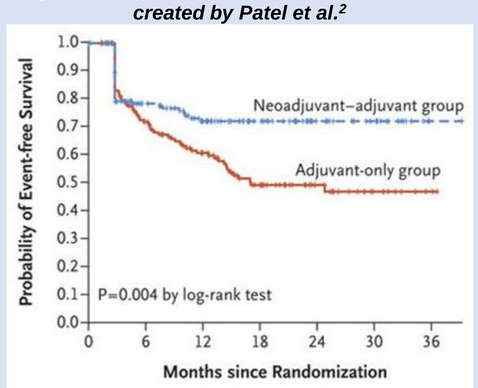
Database	Search String	Results
PubMed	Neoadjuvant therapy for stage III melanoma	151
PubMed	Neoadjuvant and adjuvant therapy for stage III melanoma	114
ASCO	Neoadjuvant and adjuvant therapy for stage III melanoma	206
JAMA Oncology	Neoadjuvant and adjuvant therapy for stage III melanoma	38

Results

Table 2: SWOG S1801 Data

	Neoadjuvant group n=154	Adjuvant group n=159
Event-free survival	72%	49%
Deaths	14	22
Treatment related adverse events (> grade 3)	12%	14%

Figure 1. Kaplan Meier curve from SWOG data created by Patel et al.[2]



- Phase II clinical trial conducted by Patel et al named SWOG S1801.[2]
- Assessment of **Neoadjuvant therapy** with PD1 inhibitor pembrolizumab prior to surgery compared to **adjuvant therapy** with pembrolizumab post-surgery.[2]
- This study showed that Neoadjuvant therapy is more effective treatment compared to adjuvant therapy.[2]
- Table 3 and 4 shows data pooled together from six trials on Neoadjuvant treatment with different therapies.[3,4,5,6,7,8,9,10]
- This showed that Neoadjuvant therapy with combination therapy is the most efficacious in producing complete pathological response.[3]

Table 3: Pooled data for pathological response created by Menzies et al [3]

Pathological response	Overall (*n* = 189) n (%, 95% CI)[a]	Targeted therapy (*n* = 51) n (%, 95% CI)[a]	Immunotherapy (*n* = 138) *n* (%, 95% CI)[a]	*P* value[b]
pCR (Complete Response)	75 (39.7%, 33–47)	24 (47%, 33–61)	51 (37.0%, 29–46)	0.017
Near pCR	21 (11.1%, 7–16)	0 (0%, 0–7)	21 (15.2%, 10–22)	
pPR (Partial Response)	27 (14.3%, 10–20)	10 (20%, 10–33)	17 (12.3%, 7–19)	
pNR (No Response)	66 (34.9%, 28–42)	17 (33%, 21–48)	49 (35.5%, 24–40)	
pCR/near pCR	96 (50.8%, 43–58)	24 (47%, 33–61)	72 (52.2%, 44–61)	0.443

a = 95% CIs are based on the Clopper–Pearson exact method

b = comparing immunotherapy to targeted therapy groups

Table 4: Pooled data for pathological response immunotherapy cohort created by Menzies et al [3]

Pathological response	Monotherapy (*n* = 35) anti PD-1 *n* (%, 95% CI)[a]	Combination (*n* = 103) ipilimumab & nivolumab *n* (%, 95% CI)[a]	*P* value[b]
pCR	7 (20.0%, 8–37)	44 (42.7%, 33–53)	< 0.001
near pCR	2 (5.7%, 1–19)	19 (18.4%, 11–27)	
pPR	3 (8.6%, 2–23)	14 (13.6%, 8–22)	
pNR	23 (65.7%, 48–81)	26 (25.2%, 17–35)	
pCR/near pCR	9 (25.7%, 12–43)	63 (61.2%, 51–71)	< 0.001

Results

- A follow-up study on 30 patients treated with Neoadjuvant therapy with PD1 inhibitor pembrolizumab performed by Sharon et al showed the efficacy of Neoadjuvant therapy over a five-year time span.[11]
- It reported a 100% 5-year Overall Survival for patients with MPR (major pathologic response) or pCR (n=8) with rest of the cohort at 72.5% (p=0.12)[11]
- Recurrence rate of 2/8 in patients with MPR or pCR and 8/22 in rest of the cohort.[11]

Discussion

Tailoring Treatment:

- The findings underscore the importance of tailoring treatment based on pathological responses, with the 5-year OS of 100% in the MPR/pCR group highlighting the potential benefits of a personalized approach in melanoma management.[11]

Long-Term Follow-Up Emphasis:

- The need for extended follow-up, especially considering the observed differences in median time to recurrence, emphasizes the importance of continuous monitoring to assess the durability and sustained impact of neoadjuvant therapy.[12]

Proposed Mechanism and Immunotherapy Efficacy:

- The efficacy of neoadjuvant therapy highlights the proposed mechanism that if the tumor contains immune cells producing an immune response, concurrent with immunotherapy, removing the tumor prior to immunotherapy administration could lead to a loss of immune cells that produce the response. This may potentially dampen the effect of immunotherapy, suggesting a nuanced consideration of timing in treatment planning.[13]

Future Directions

Biomarker Identification:

- Efforts could be directed towards identifying robust biomarkers that predict response to neoadjuvant immunotherapy, aiding in patient selection and personalized treatment plans. This may involve comprehensive molecular profiling and immune cell characterization within the tumor microenvironment.[14]

Integration with Emerging Therapies:

- The integration of neoadjuvant immunotherapy with emerging therapies, such as targeted therapies or other immunomodulatory agents, could be explored further. This multifaceted approach may enhance treatment responses and broaden therapeutic options.[15]

Health Economic Assessments:

- Future work may involve health economic assessments to evaluate the cost-effectiveness of neoadjuvant strategies, considering the potential reduction in disease recurrence and long-term healthcare costs. This information could inform healthcare policies and resource allocation.