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Immunotherapy Toxicities in Advanced Melanoma: A Real-World Analysis

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Abstract

Aims

In melanoma, immunotherapy has improved survival but can be associated with significant toxicity. We assessed real-world outcomes in a tertiary cancer centre.

Methods

We reviewed charts of all metastatic melanoma patients who received nivolumab/ipilimumab (nivo/ipi, n=16) or single-agent ipilimumab (n=19) (2015-2020).

Results

Patients receiving nivo/ipi had a greater number of grade 3-4 toxicities than those on ipilimumab alone (p=0.002). 44% of those receiving nivo/ipi and 16% receiving ipilimumab had any grade 3+ toxicity (p=0.07). Grade 3+ colitis was reported only with ipilimumab alone (n=3, 16%), while nivo/ipi patients reported colitis (n=1, 3%), hepatitis (n=3, 19%), adrenalitis and nephritis (n=2, 13% each), pneumonitis, dermatitis, hypophysitis and hearing loss (n=1, 6% each). Overall, 29% of patients had delays due to AEs, and 23% stopped treatment due to AEs. With single-agent ipilimumab, median PFS was 3.3 months (95% CI 1.3-5.3), OS was 39 months (95% CI 21.3-47.9). With nivo/ipi, median PFS was 4.6 months (95% CI 0-9.9), median OS was not reached (median followup 58.3 and 18.4 months for single-agent and nivo/ipi groups).

Conclusion

Toxicities were significant but comparable to previous studies. Further follow-up is needed to compare local survival outcomes to international data.

Keywords: melanoma; immunotherapy; immunotoxicity

Introduction

Melanoma is a commonly occurring skin cancer, with approximately 1,200 new cases per year in Ireland[1], accounting for 3% of all new cancer diagnoses[2]. Ireland now has the 9th highest incidence in Europe, with an age-adjusted incidence of 30.5 cases/100,000 people, compared to a European average of 23 cases/100,000[1].

Though most cases present early, 20% of men and 14% of women have advanced (stage 3-4) disease at diagnosis[1]. Up until very recently, treatments for stage 4 disease have been very limited, with a median progression free survival (PFS) of 8 months and a 5 year survival of <10%[3], and until 2011, no agents were available with proven overall survival (OS) benefit[3]. Since then, several targeted therapies (BRAF and MEK inhibitors) and immunotherapies (CTLA-4, anti PD-1) have become available.

Following HSE funding approval in 2012, ipilimumab, an anti–cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) fully human monoclonal antibody, became the standard of care, with a 10 year OS of approximately 20%[4]. Subsequent studies have shown that anti–programmed death 1 (PD-1) agents, such as nivolumab or pembrolizumab, have superior OS, PFS, and response rate than ipilimumab alone[4]. Current European Society of Medical Oncology (ESMO) guidelines support first-line use of an anti PD-1 ± ipilimumab, in the absence of contraindications, independent of PD-L1 status[5].

The phase 3 CheckMate 067 trial[4,6] examined 3 possible strategies: (a) nivolumab plus ipilimumab every 3 weeks for four doses, followed by nivolumab every 2 weeks; (b) nivolumab every 2 weeks; or (c) ipilimumab every 3 weeks for four doses. Median OS was more than 5 years in the nivolumab/ipilimumab combination group, and 19.9 months in the ipilimumab group. OS at 5 years was 52% in the combination group, and 26% in the ipilimumab group. The median PFS was 11.5 and 2.9 months, with five-year PFS of 36% and 8% in the combination and ipilimumab groups, respectively[6].

Despite the survival benefits seen, dual-immunotherapy treatment was associated with significant toxicity. 96% of combination therapy patients and 86% ipilimumab-alone patients had a drug-related adverse event (AE); with grade 3 or higher AEs in 59% and 28% respectively. Treatment-related AEs that led to drug discontinuation were frequent (39% and 16%). The most common any-grade AEs were skin-related (62% in combination therapy, 56% in ipilimumab monotherapy). Endocrine disturbances also occurred (hypothyroidism: 17%, 5%; hyperthyroidism: 11%, 1%; hypophysitis: 7%, 4% in combination and single-agent ipilimumab respectively), often requiring long-term hormone replacement. Common grade 3+ AEs included colitis (8%, 8%), hepatitis (9%, 2%), and pneumonitis (1%, <1% respectively)[4].

More recent real-world analysis has found grade 3+ toxicities in 60%[7], with early drug discontinuation rates varying between 20%[8] and 60%[7] for combination treatment. Irish retrospective studies of ipilimumab alone have found grade 3+ toxicity in approximately 30%[9,10], with only 59% of patients receiving all planned cycles[11].

Assessment of disease response can be more complicated in immunotherapy, as immunotherapies occasionally trigger a tumour flare reaction (pseudoprogression), causing a transient increase in a lesion size, and simulating a progression of the disease on imaging. This can occur in 10-20% of patients[12], and for this reason, patients are sometimes continued on treatment after an apparent progression on early imaging.

Prior to CheckMate 067, our local practice had been to treat with single-agent ipilimumab three-weekly for four doses, followed by surveillance[13]. In Ireland, funding for cancer therapies is centrally approved by the government, and drugs are only available for specified indications. When combination treatment became approved for funding (2017), where appropriate we have given nivolumab and ipilimumab three-weekly for four doses, followed by nivolumab maintenance[14], or single-agent anti PD-1 (pembrolizumab/nivolumab), with single-agent ipilimumab now rarely used. We aimed to assess the tolerability and toxicity of ipilimumab in a real-world setting.

Methods

A retrospective chart review was performed of all metastatic melanoma patients in a tertiary cancer centre (St James's Hospital, Dublin) who received either combination (nivolumab/ipilimumab, n=16) or single agent (ipilimumab, n=19) immunotherapy from 2015 to May 2020, assessing rates of immune-related adverse events (CTCEA version 5.0) and outcomes.

The review was overseen by the St. James's/Tallaght university hospital joint research ethics committee. Charts were reviewed by a medical intern and an oncology registrar.

Where patients had early radiological evidence of disease progression, later scans and MDT discussions were reviewed to differentiate between true progression and pseudo-progression.

Survival analysis (Kaplan–Meier) and univariate analysis of associations was performed in IBM SPSS Statistics for Windows, Version 27. Where appropriate, differences between categorical variables were analysed by χ^2 tests, and numerical variables with t-tests.

Results

Demographics

Of the 35 patients treated (median age 59.1, range 28-82), 26% were BRAF V600E mutant and 3% (n=1) had a mutation of unknown significance (BRAF p.G469A). BRAF status was known in 89% at the start of treatment. 89% had not previously had systemic therapy. 9% had a history of autoimmune disease; mean Charlson comorbidity score was 7.6 (range 6-11). These did not independently predict toxicity and were similar between single and combination treatment groups (see table 1). Patients on single-agent therapy had longer follow up times.

Table 1. *Patient demographics and outcomes.*

	Single-agent (n=19)	Combination (n=16)	p value
Age (median, SD)	59.4 (14.4)	58.7 (11.0)	0.9[a]
BRAF wild-type (n, %)	14 (82%)	11 (69%)	0.3[b]
Previous treatment (n, %)	2 (11%)	2 (13%)	0.9[b]
Charlson co-morbidity score (median, SD)	7.5 (1.7)	7 (1.1)	0.5 [a]
Autoimmune disease (n, %)	2 (11%)	1 (6%)	0.7[b]
Follow up duration (months; median, SD)	58.3 (8.7)	18.4 (7.8)	<0.01[a] *
Number of cycles completed (mean, SD)	3.1 (1.2)	3.1 (1.3)	0.9 [a]
Treatment delayed due to AE (n, %)	3 (16%)	7 (44%)	0.07[b]
Treatment stopped due to AE (n, %)	3 (16%)	5 (31%)	0.3[b]
Experienced any grade 3+ toxicity (n, %)	3 (16%)	7 (44%)	0.07[b]
Experienced multiple grade 3+ toxicities (n, %)	0 (0%)	2 (13%)	0.1[b]
Number of grade 3+ toxicities/patient (mean, SD)	0.2 (0.4)	0.6 (0.9)	0.04 [a] *
[a]t-test [b]chi-squared test * significant p value			

Toxicities

Only 40% of patients completed 4 cycles as planned. The average number of cycles received was 3.1. 28.6% had treatment delays due to AEs (43.8% (combination) v 15.8% (single agent), p=0.07, OR 4.1, 95% CI 0.9-20.1), 22.9% stopped due to AEs (31.2% vs 15.8%). Of those who had died (n=13), 38.5% had received treatment in the 30 days before their death.

Patients on combination treatment had a greater number of severe (grade 3-5) toxicities than those on single agent treatment (mean number 0.63 vs 0.16, p=0.04). Common any-grade toxicities included hypothyroidism (25.7%), hyperthyroidism (5.7%), colitis (22.9%), and hepatitis (11.4%). 43.8% of patients on combination and 15.8% on single-agent therapy developed a grade 3/4 immunotoxicity (28.5% overall, p=0.07, OR 4.1, 95% CI 0.9-20.1) (Table 2). Two (12.5%) combination treatment patients had multiple grade 3+ toxicities.

Table 2. *Severe (grade 3) toxicities by treatment type.*

	Colitis	Hep.	Adr.	Nephritis	Pneum.	Derm	Hypophysitis	SNHL
Single (n,%)	3 (15.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Com. (n,%)	1 (2.9)	3 (18.8)	2 (12.5)	2 (12.5)	1 (6.3)	1 (6.3)	1 (6.3)	1 (6.3)
Total (n,%)	4 (11.4)	3 (8.6)	2 (5.7)	2 (5.7)	1 (2.9)	1 (2.9)	1 (2.9)	1 (2.9)
Single: ipilimumab, Com: combination nivolumab/ ipilimumab. Adr: adrenalitis, Pneum: pneumonitis, Derm: dermatitis/severe rash, SNHL: sensori-neural hearing loss								

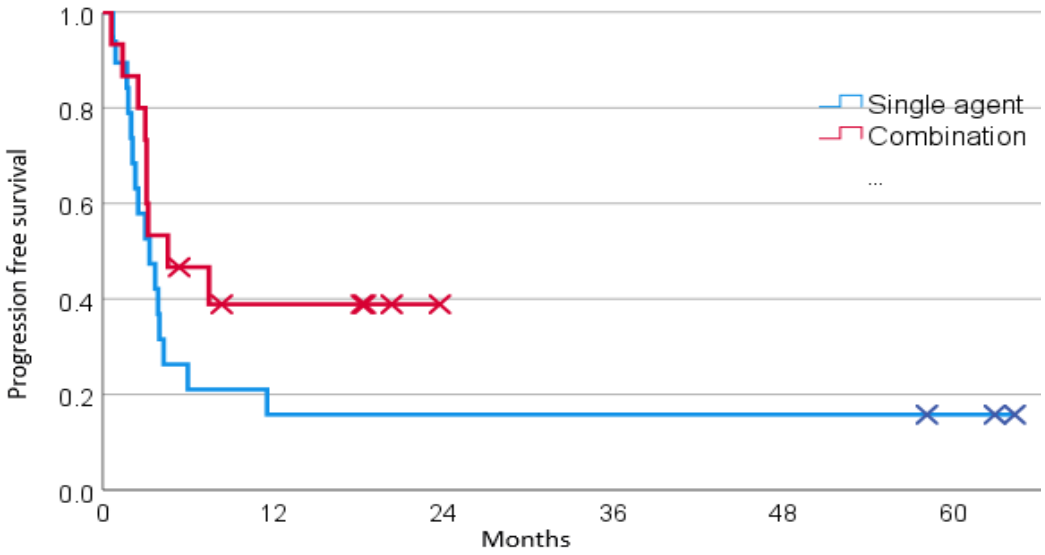
Progression free and overall survival

In single-agent treatment, at a median follow up of 58.3 months after the first dose (interquartile range (IQR): 52.6-63 months), median PFS was 3.3 months (95% CI 1.6-5.0 months, fig. 1), median OS was 39 months (95% CI 21.3-47.9, fig. 2). Only 3 patients receiving single agent ipilimumab had PFS of more than a year, but all of these showed durable response at 4 years (5-year PFS of 12.5%).

In combination treatment, at a median follow up of 18.4 months after the first ipilimumab (IQR: 8.6-20.1 months), median PFS was 4.6 months (95% CI 0-9.9 months), median OS has not been reached. 1 patient had severe renal toxicity and so was unable to be restaged on schedule, he showed progression at first restaging (5 months post-treatment) but is not included in the PFS analysis.

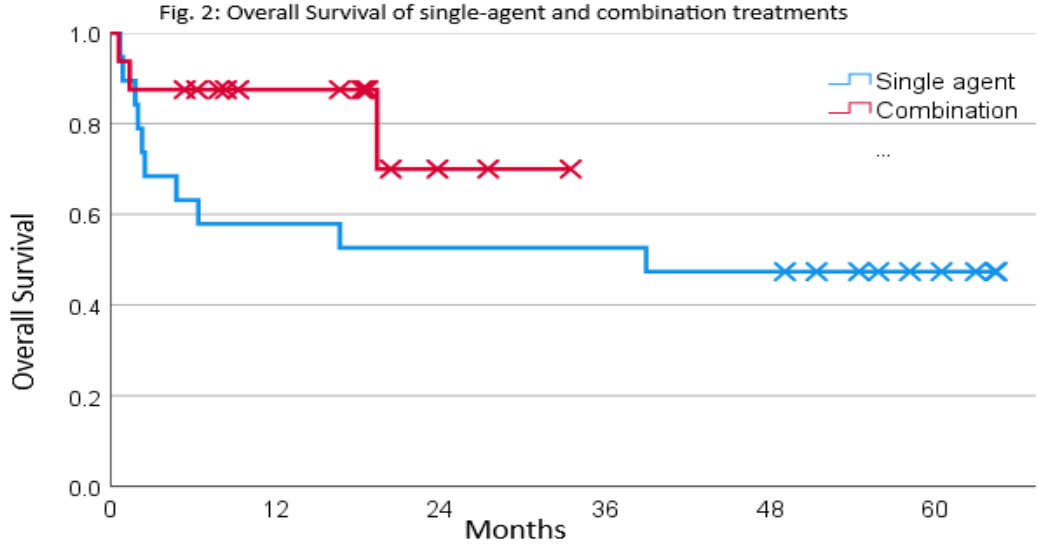
No significant difference was seen between single-agent and combination groups in terms of progression-free survival (log-rank p=0.16) or overall survival (log-rank p=0.14) (Fig. 1 and 2).

Fig. 1 : Progression Free Survival of single-agent and combination treatments



Number at risk						
Single agent`	19	3	3	3	3	2
Combination	15	4	0	0	0	0

Fig. 2: Overall Survival of single-agent and combination treatments



Number at risk						
Single Agent	19	11	10	10	9	4
Combination	16	9	2	0	0	0

Those with severe immunotoxicities had a median PFS of 7.5 months (95% CI 0-16 months), compared to 3.2 months in those who did not (95% CI 2.8-3.6 months) (p=0.3).
Pseudoprogression was not observed.

Discussion

Both single-agent and combination immunotherapies were well tolerated by the majority of patients, with toxicity profiles similar to that seen in CheckMate 067[4,6]. Some individual grade 3+ AEs were more common than in CheckMate, with hepatitis rates in the combination group of 18.8% (9% in CheckMate), adrenalitis and nephritis 12.5% each (not specified in CheckMate but known to occur with immunotherapies). Some AEs were likely irreversible (e.g. hypophysitis).

While patients receiving combination treatment were numerically more likely than those on single-agent to have a severe toxicity (43.8% vs 15.8%) or discontinue treatment because of toxicity (31.2% vs 15.8%), this did not reach significance. This may have been related to the comparatively small number of patients in our study (n=35). It is possible that as some combination patients had only recently finished ipilimumab (19% within the last six months) that delayed toxicities may yet develop[15].

Our median OS was longer for single agent patients than in the CheckMate data (39 vs 19.9 months), but our PFS and 5-year PFS were comparable. This may reflect improvements in second-line treatments since CheckMate stopped enrolling in 2014.

Our combination treatment median PFS, at 4.6 months, is shorter than the 11.5 months seen in CheckMate 067[4,6]. This may be related to immaturity of the data; of those who achieved 6 months of progression-free survival, 75% maintained response, and in other studies a significant number of patients see sustained response, prolonging the median PFS. Overall, all who had response at 1 year (both single agent and combined, total n=7) maintained response without further systemic treatment.

No survival differences were yet shown between single and dual immunotherapy, which may reflect immaturity of the data.

The slightly higher median PFS of 7.5 months in those with grade 3 toxicities, compared to 3.2 months in those without, is in keeping with previous work which has found that toxicity may be associated with greater treatment response[9,16], but longer follow up may be needed to demonstrate stronger associations.

The rates of toxicity seen were significant, but generally consistent with existing safety information. Patients and clinicians need to be aware of the possibility of life-threatening or irreversible toxicity. Further follow up is needed to assess our local survival outcomes in combination nivolumab/ipilimumab treated patients in comparison to international data.

Declaration of Conflicts of Interest:
The authors have no conflicts of interest to declare.

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