Sociedad Andaluza de Oncología Medica

I Reunión de manejo de los efectos secundarios inmunomediados
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Guías y aspectos centrales en el manejo de las toxicidades inmunomediadas

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NCCN CLINICAL PRACTICE GUIDELINES IN ONCOLOGY

Management of Immunotherapy-Related Toxicities, Version 1.2019

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CLINICAL PRACTICE GUIDELINES

An ESMO Product

Management of toxicities from immunotherapy

ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

J. Haanen, F. Carbonnel, C. Robert, K. Kerr, S. Peters, J. Larkin and K. Jordan,
on behalf of the ESMO Guidelines Committee

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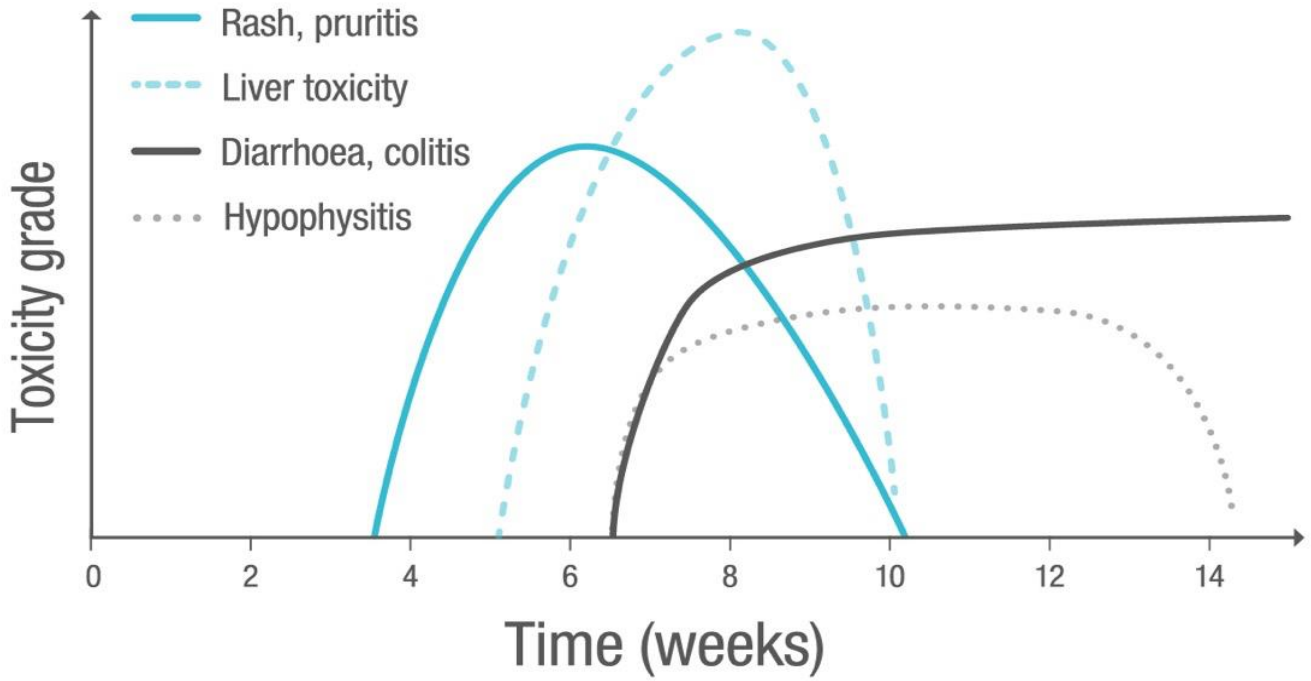
ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

CLINICAL PRACTICE GUIDELINES

Incidence and epidemiology

Time to onset and resolution of occurrence of immuno-related adverse events following Ipilimumab treatment



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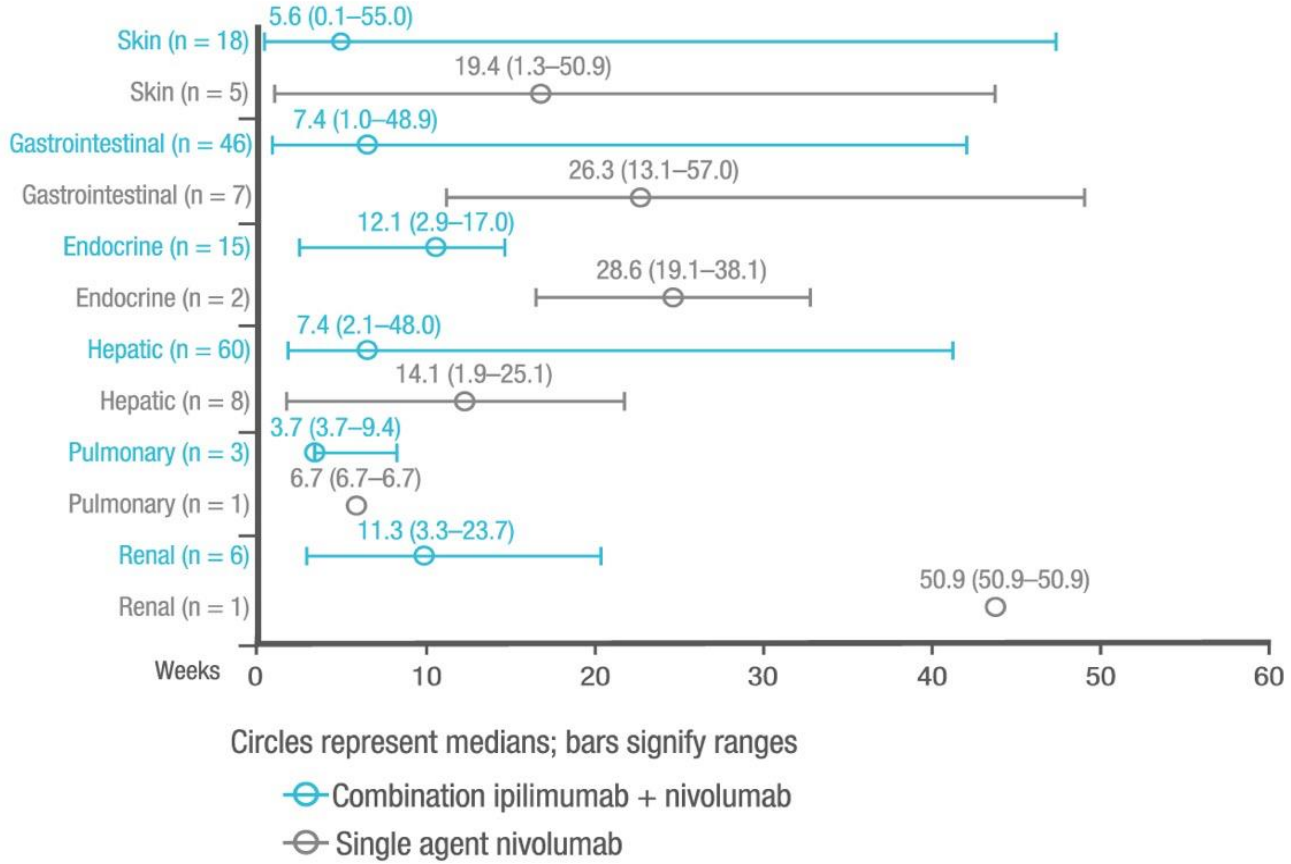
CLINICAL PRACTICE GUIDELINES

Incidence and epidemiology

Time to onset of grade 3-4 treatment-related select adverse events



Larkin J et al. Presented at ECC 2015;Abs330.
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CLINICAL PRACTICE GUIDELINES

Incidence and epidemiology

Summary of recommendations	
General aspects of immune-related adverse events (irAEs)	Generally occur within 3 months after initiation of ICPi treatment
	Tissue biopsy may be useful for higher grade (3-4) toxicities, when there is diagnostic doubt and management would be altered by the outcome
Patient selection and baseline assessments	Before starting treatment: patients' susceptibility to irAEs should be assessed and patients informed of the potential AEs, reporting directly to the treating physician or team
	Work-up should include: history, general physical condition, autoimmune diseases, baseline laboratory tests and radiological scans • If current or previous autoimmune disease: risk of worsening of their autoimmune disease while on ICPi treatment • If previous ipilimumab-related irAEs: risk of developing irAEs following anti-PD-1 treatment, and vice versa
	Once irAEs have developed, prompt work-up and action are required
	Pneumocystis prophylaxis should be considered for patients receiving long-term (> 6 weeks) treatment with immunosuppressive drugs
	The clinical outcome of patients on ICPi treatment is not affected by the use of immunosuppressive agents for the management of immune-related toxicities

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ESTUDIOS A REALIZAR EN TODO PACIENTE ANTES DEL INICIO DE TRATAMIENTO CON INMUNOTERAPIA

Hº clínica: reflejar antecedentes personales de:

- *Enfermedades autoinmunes*
- *Enfermedades infecciosas*
- *Enfermedades dermatológicas*
- *Enfermedades endocrinológicas*
- *Hábito intestinal: frecuencia de defecación y consistencia de heces*

Exploración clínica

- *Bocio y pulso para la valoración tiroidea.*
- *Examen completo de la piel y mucosas.*

Análisis de sangre:

- *Hemograma y bioquímica con iones.*
- *HbA1*
- *Perfil lipídico*
- *TSH, T4L, Ac antiTPO*
- *CPK total*
- *HBAg; HBAc; BBcAc; HCAc; CMV Ac; VIH Ac; VIH Ag (p24) Test T-spot*

Función pulmonar:

Saturación de oxígeno en reposo y durante la deambulación

Función cardiaca:

- ECG

- Troponina I o T

Pacientes con enfermedad previa o de alto riesgo de toxicidad

Endocrino: Cortisol y ACTH a las 8H*
Cardiología: BNP o NT pro-BNP
Neumología: Test de función respiratoria y 6MWTc

***Importante:**
-Determinar siempre Cortisol, T4L junto a TSH.
- ACTH precisa tubo con EDTA y enviar rápidamente a laboratorio.

Albero Tamarit A, Mediano Rambla MD, de la Cruz-Merino L. Inmunooncomecum 2019

Table 2 General guidance for corticosteroid management of immune-related adverse events

Grade of immune-related AE (CTCAE/equivalent)	Corticosteroid management	Additional notes
1	Corticosteroids not usually indicated	• Continue immunotherapy
2	• If indicated, start oral prednisone 0.5-1 mg/kg/day if patient can take oral medication. • If IV required, start methylprednisolone 0.5-1 mg/kg/day IV • If no improvement in 2–3 days, increase corticosteroid dose to 2 mg/kg/day • Once improved to ≤grade 1 AE, start 4–6 week steroid taper	• Hold immunotherapy during corticosteroid use • Continue immunotherapy once resolved to ≤grade 1 and off corticosteroids • Start proton pump inhibitor for GI prophylaxis
3	• Start prednisone 1-2 mg/kg/day (or equivalent dose of methylprednisolone) • If no improvement in 2–3 days, add additional/alternative immune suppressant • Once improved to ≤ grade 1, start 4–6-week steroid taper • Provide supportive treatment as needed	• Hold immunotherapy; if symptoms do not improve in 4–6 weeks, discontinue immunotherapy • Consider intravenous corticosteroids • Start proton pump inhibitor for GI prophylaxis • Add PCP prophylaxis if more than 3 weeks of immunosuppression expected (>10 mg prednisone or equivalent/day)
4	• Start prednisone 1-2 mg/kg/day (or equivalent dose of methylprednisolone) • If no improvement in 2–3 days, add additional/alternative immune suppressant, e.g., infliximab • Provide supportive care as needed	• Discontinue immunotherapy • Continue intravenous corticosteroids • Start proton pump inhibitor for GI prophylaxis • Add PCP prophylaxis if more than 3 weeks of immunosuppression expected (>10 mg prednisone or equivalent/day)

Note: For steroid-refractory cases and/or when steroid sparing is desirable, management should be coordinated with disease specialists. AE, adverse event

Grado	Tratamiento	Fármaco diana
1	Tratamiento sintomático	Continuar
2	Corticoides orales	Suspensión temporal
3	Corticoides iv/tto inmunosupresor	Suspensión temporal/definitiva
4	Corticoides iv/tto inmunosupresor	Suspensión definitiva

DOSIS DE CORTICOIDES Y REINICIO DE FÁRMACO DIANA TRAS SUSPENSIÓN

- Si el paciente está con tratamiento corticoideo oral y empeora se pautará iv.
- El tratamiento iv se mantiene hasta G2. Pasar entonces a prednisona oral
- Los corticoides orales se mantienen hasta G1(según gravedad alcanzada, la duración del tratamiento se prolongará durante 4-8 semanas)
- Si el paciente empeora se reescalan dosis.
- SE REINICIARÁ EL FÁRMACO DIANA cuando el paciente esté asintomático y con dosis de prednisona oral <10 mg/día

- **La toxicidad exige una vigilancia intensa y puede empeorar rápidamente**
- **Parece importante que los pacientes identifiquen pronto la toxicidad para inicio de medidas terapéuticas**
- **Hay que realizar un diagnóstico diferencial**

Tratamiento adicional a los corticoides
Desde el inicio
Inhibidor de la bomba de protones
Si va a precisar más de 3-4 semanas de tratamiento con dosis de 20 mg/día de prednisona o equivalente

- Suplementos de Vitamina D y calcio
- Profilaxis de Peumocystis con cotrimoxazol 480 mg/12h los lunes, miércoles y viernes o pentamidina inhalada si alergia.

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Therapy	Common Schedules	irAE	Evidence Level/ Recommendation Grade
Corticosteroids	Oral prednisone 1-2 mg/kg. IV methylprednisolone 125-1000 mg/day	From grade ≥2 irAEs, in any toxicity	III/ C
Anti-TNFα	Infliximab 5 mg/kg once every 2 weeks	CRT, especially in colitis and pneumonitis	III/ C
Anti-IL6	Tocilizumab 8 mg/kg iv once per month	CRT, alternative to anti-TNFα, especially in myocarditis	IV/ D
Anti-IL1	Anakinra 100 mg once per day or canakizumab 300-600 mg once every 8 weeks	CRT, alternative to anti-TNFα, especially in myocarditis	IV/ D
Mycophenolate	500 mg orally twice a day	CRT, especially in hepatitis	III/ C
Anti-CD20	Rituximab 375 mg/m2 iv once weekly for 4 weeks	Multirefractory toxicity, especially in SLE, Sjögren syndrome, nephritis, encephalitis and others	IV/ D
Immunoglobulins	Immunoglobulins iv 400 mg/kg per day, 5 days	GBS, MG, encephalitis and other neurological irAEs	IV/ D
Plasmapheresis	Several courses as needed	GBS, other neurological irAEs	IV/ D

Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: SEOM Clinical Practice Guideline. Clin Transl Oncol. Epub Ahead of Print

LA ORACIÓN DE MAIMÓNIDES

...Haz que sea modesto en todo excepto en el deseo de conocer el arte de mi profesión. No permitas que me ataque el pensamiento de que ya sé bastante. Por el contrario, concédeme la fuerza, la alegría y la ambición de saber más cada día. Pues el arte es inacabable, y la mente del hombre siempre puede crecer....