

Management toxicity pri liečbe alemtuzumabom – Európske odporúčania

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- Konsenzus stretnutia expertov - update managementu a guidelines - alemtuzumab pri CLL
- Update guidelines z roku 2004 – na základe širších skúseností pri liečbe alemtuzumabom v súčasnosti

1. Alemtuzumab v monoterapii – bezpečné použitie v 1.línii liečby
2. Pacienti vhodní na liečbu alemtuzumabom – del 17p, starší pacienti, pacienti s refraktérnou cytopéniou/cytopéniami autoimúnneho pôvodu alebo ak ide o cytopéniu ako dôsledok výraznej infiltrácie KD
3. Liečba alemtuzumabom by mala optimálne trvať 12 týždňov (36 dávok) s následným vyšetrením KD za účelom hodnotenia liečebnej odpovede

4. PCR monitoring CMV reaktivácie - á týždeň - počas terapie alemtuzumabom; ak je CMV reaktivácia symptomatická alebo dochádza ku vzostupu kvantity virémie, liečba alemtuzumabom – prerušenie + nasadenie anti-CMV terapie
5. Subkutánná aplikácia je bezpečná, management je jednoduchý a je rovnako efektívna ako intravenózna infúzia
6. Alemtuzumab v kombinácii a v konsolidačnej liečbe – len v rámci kontrolovaných klinických skúšaní

Recommendations

Treatment duration	12 weeks
Route and dosage	s.c. 30 mg t.i.w. after optional dose escalation
Response assessment	1. Regular clinical examination (e.g., lymphocyte count, lymph node, organomegaly, B symptoms) 2. Bone marrow biopsy at week 12
Suitable patient population	1. Elderly patients (aged >65 years) 2. Patients with 17p deletion 3. Patients with pancytopenia due to heavily infiltrated bone marrow 4. Patients with autoimmune hemolytic anemia or autoimmune thrombocytopenia

- “Prechodná „first-dose“ kožná reakcia vyskytujúca sa pri s.c. aplikácii → predĺženie intervalu eskalácie dávky na 2 týždne; ostatné nežiadúce reakcie spojené s „first-dose“ aplikáciou sú zriedkavé alebo chýbajú (subfebrility)

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- Na základe týchto údajov – je doporučená – s.c. aplikácia alemtuzumabu, ktorá by mala nahradiť i.v. podanie.
- Doporučené dávkovanie s.c. aplikácie alemtuzumabu je identické ako pri i.v. podaní (30mg 3 dni v týždni, v celkovom počte 36 dávok v trvaní 12 týždňov). Iný režim dávkovania sa nedoporučuje.
- Doba do eskalácie dávky môže byť predĺžená do 2 týždňov v prípade výskytu symptomatickej lokálnej kožnej reakcie.

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- Úroveň evidencie: nerandomizované klinické skúšania
- Odkazy na literatúru:
 - Hillmen P, et al. *J Clin Oncol* 2007; 25: 5616–5623.
 - Lundin J, et al. *Blood* 2002; 100: 768–773.
 - Stilgenbauer S, et al. *Blood* 2008; 112: 127.
 - Karlsson C, et al. *Br J Haematol* 2009; 144: 78–85.
 - Hwang W, et al. *Blood* 2006; 108: 336b.
 - Wierda WG, et al. *Blood* 2006; 108: 804a.

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- Toxicita je dôležitý faktor, ktorý determinuje terapeutický plán pre starších pacientov s CLL. Fludarabín, ktorý má vysoký počet liečebných odpovedí, je však niekedy zo strany starších pacientov horšie tolerovaný. Okrem toho v klinickej štúdií German CLL5 fludarabin versus chlorambucil v 1.línii u starších pacientov nebol zaznamenaný benefit v celkovom prežívaní v prospech fludarabínu.
- Na druhej strane alemtuzumab u starších pacientov dosahuje vysoký počet liečebných odpovedí bez výraznejšej neakceptovateľnej toxicity (vhodný u starších pacientov s cieľom dosiahnutia remisie ochorenia alebo u skupiny pacientov s agresívnym ochorením).

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 - Lundin J, et al. *Blood* 2002; 100: 768–773.
 - Eichhorst BF, et al. *Blood* 2007; 110: 194a.

Recommendations

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- Neutropénia, trombocytopénia a závislosť na transfúziách, ktoré vyplývajú zo závažnej infiltrácie KD a/alebo predchádzajúcej liečby môžu byť problémom pri následnej liečbe cytotoxickou chemoterapiou.
- Alemtuzumab dosahuje remisiu v KD bez výraznejšej hematologickej toxicity.

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- Pre vybranú skupinu pacientov s pancytopéniou prítomnou pred samotnou liečbou, ktorá je spôsobená závažnou infiltráciou KD, môže byť použitie alemtuzumabu zvažované v 1.línii liečby.
- Úroveň evidencie: empiria

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- Účinnosť alemtuzumabu bola dokázaná u refraktérnej AIHA a ITP – CLL.
- Úroveň evidencie: kazuistiky, menšie skupiny pacientov

Recommendations

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- Napriek tomu, že samotný alemtuzumab môže spôsobiť AIHA (podľa produktových údajov), doporučuje sa jeho použitie u pacientov s AIHA a ITP, ktorí neodpovedajú na konvenčnú liečbu.
- Alemtuzumab je liekom voľby pre pacientov s aktívnou autoimunitou, ktorí majú progredujúcu CLL indikovanú na liečbu.

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- Odkazy na literatúru:
 - Barcellini W, et al. *Haematologica* 2006; 91: 1689–1692.
 - Karlsson C. *Leukemia* 2007; 21: 511–514.
 - Laurenti L, et al. *Leukemia* 2007; 21: 1819–1821.

Recommendations

Patient management

Hematologic events	Refer to alemtuzumab prescribing information for treatment interruption and dose modification. ²⁷ Use supportive therapy (G-CSF or irradiated blood product) when indicated
Infections	Cotrimoxazole prophylaxis for <i>P. jirovecii</i> pneumonia and aciclovir prophylaxis for herpes virus
CMV reactivation	Clinical watch and weekly CMV test Refer to O'Brien <i>et al.</i> ²⁸ for treatment of CMV reactivation
Infusion-related events	Antihistamine and acetaminophen premedication Corticosteroid prophylaxis is recommended, but at week 1 only
Injection-site skin reactions	Antihistamine and acetaminophen premedication Corticosteroid prophylaxis is recommended, but at week 1 only

- Granulocyte colony-stimulating factor (G-CSF) – podporná liečba sa doporučuje ANC < 0,5.10⁹/l.
- Ožiarené krvné prípravky (potenciálna s transfúziou spojená graft-vs-host disease) – u pacientov so závažnou lymfopéniou.

Recommendations

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- Profylaxia cotrimoxazolom (alebo inhalačným pentamidinom u pacientov, ktorí sú alergickí na cotrimoxazol) sa doporučuje v trvaní 6 mesiacov od ukončenia liečby alemtuzumabom (minimalizácia rizika pneumocystovej pneumónie – *P.jirovecii*)
- Profylaxia acyclovirom sa doporučuje v trvaní 6 mesiacov od ukončenia liečby alemtuzumabom (minimalizácia rizika reaktívacie závažnej herpetickej infekcie)
- Úroveň evidencie: empirická

Recommendations

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- Monitorig CMV reaktivácie q-PCR á týždeň – počas liečby alemtuzumabom.
- Prísne klinické sledovanie event. prvých príznakov CMV reaktivácie (subfebrility, slabosť, ↑ CRP)

Recommendations

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- Pacienti s febrilitami a negatívnou CMV PCR analýzou – vyšetrenia zamerané na iné patogény; vrátane CT pľúc, bronchoskopia+BAL (Pneumocyst., adenovírusy, EBV a iné).
- Úroveň evidencie: empirická

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- Profylaxia valgancyclovirom - na základe rozhodnutia lekára u pacientov so zvýšeným rizikom CMV reaktivácie
- Pravidelné sledovanie pacientov – riziko myelosupresie

Management pacientov - doporučenia

genzyme

Recommendations

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- p.o. premedikácia antihistaminikom a acetaminophenom – pred infúziou
- kortikosteroidy (p.o. alebo i.v.) – týždeň 1.-2.
- triaške – prerušenie infúzie a i.v. podanie pethidinu
- antiemetiká – nauzea pri pethidine
- rash – pridanie p.o. antihistaminika á 4 hod. a p.o. kortikoidov
- u pacientov so závažnou infusion-related toxicitou – premedikácia i.v. HDC
- kortikosteroidy by mali byť taperované čím skôr (1-2 t)

Management pacientov - doporučenia

genzyme

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- s.c. podanie alemtuzumabu – lokálna kožná reakcia (erytém a edém)
- profylaxia - identická ako pri i.v. aplikácii

Alemtuzumab v monoterapii – bezpečné použitie

Alemtuzumab v kombinácii a v konsolidačnej liečbe – len v rámci kontrolovaných klinických skúšaní

Bezpečnostný profil bol stanovený a referovaný na základe mnohých klinických skúšaní (o.i. GOELAMS)

Ďakujem za pozornosť