PROPHYLAXIE DES NEUTROPENIES CHIMIO-INDUITES

1. Généralités

La prophylaxie des neutropénies repose sur les facteurs de croissance hématopoïétiques (FCH). Pour la prophylaxie de la neutropénie fébrile, on peut se poser la question d'y associer une antibioprophylaxie.

Grade 1	
Grade 2	
Grade 3	Polynucléaires neutrophiles < 1000/mm^3 associés à une prise de température unique > 38,3°C ou une température se maintenant ≥ 38°C pendant plus d'une heure.
Grade 4	Conséquences vitales ; nécessité de mesures de réanimation.
Grade 5	Décès.

Tableau 9 – Cotation des neutropénies fébriles selon la classification CTCAE v5.0

Les FCH sont utilisés dans les situations de prophylaxie ou de traitement des neutropénies fébriles (28,29). La prise en charge des neutropénies fébriles n'est pas abordée dans ce document. En oncologie thoracique, les FCH n'ont pas de place dans d'autres indications, **notamment dans le traitement des neutropénies *non* fébriles** (30). Les résultats thérapeutiques des FCH sont controversés. S'il est prouvé que leur utilisation diminue la fréquence, l'intensité et la durée des neutropénies et des neutropénies fébriles, ils n'ont pas apporté de preuve sur la réduction de la mortalité globale ou de la mortalité par infection, possiblement en raison de la relative rareté de ces complications graves en cancérologie pulmonaire.

En France, les FCH existent sous la forme du *Granulocyte Colony-Stimulating Factor* (G-CSF) et sous sa forme pegylée. Plus récemment sont apparus les formes biosimilaires (cf. **Tableau 10**).

En oncologie thoracique, les deux formes peuvent toutefois trouver leur place dans des situations différentes, en lien avec le type de protocole utilisé (avec ou sans J8, durée de l'intercure notamment). Il n'est en effet pas recommandé d'utiliser les FCH de manière concomitante à l'administration des produits de chimiothérapie. L'administration de FCH n'a jamais été validée lors de schémas de chimiothérapie hebdomadaires ou entre les J1 et J8 pour les protocoles en deux injections. De ce fait, il est recommandé de proposer des adaptations de la posologie des cytotoxiques. L'utilisation de FCH doit être l'exception dans ce contexte.

Les effets secondaires les plus fréquents des FCH sont :

- Les douleurs au point d'injection et les réactions d'hypersensibilité,
- Les douleurs osseuses qui sont fréquentes (10-30%). Il convient de prévenir le patient et de suggérer la prise d'antalgiques standards de pallier 1. L'âge inférieur à 45 ans et des antécédents de douleurs osseuses sont des facteurs de risque de survenue de telles douleurs (31).
- Le risque de survenue d'une leucémie aiguë myéloïde ou d'un syndrome myélodysplasique exceptionnel (32), et de très rares cas de rupture de rate ont été signalés.

Les recommandations d'utilisation des FCH ont été actualisées en 2015 par l'ASCO (30), en 2016 par l'ESMO/MASCC (33), et en 2017 par le NCCN (34).

L'efficacité des différents FCH est considérée comme équivalente et le choix dépend de la situation clinique (type de chimiothérapie) et de leur disponibilité respective (30).

DCI	Nom Commercial	Posologie	Forme	Remarque
Lénograstim rHu G-CSF	GRANOCYTE®	150 µg/m²/j SC 24h après la fin de la chimiothérapie et jusqu'à restauration du compte cellulaire (sans dépasser 28j)	A reconstituer	Produit par la technique de l'ADN recombinant dans des cellules d'ovaire de hamster chinois (CHO)
Filgrastim Facteur methionylé rHu G-CSF (35)	ACCOFIL®* BIOGRASTIM®* NEUPOGEN® NIVESTIM®*[c] RATIOGASTRIM®* TEVAGRASTIM®* ZARZIO®* TEVAGRASTIM®*	5 µg/kg/ j SC entre J+1 et J+3-4 après la fin de la chimiothérapie et jusqu'à la période du post-nadir	Seringues préremplies	Produit par la technique de l'ADN recombinant sur *Escherichia coli*
Pegfilgrastim	NEULASTA® PELGRAZ®* PELMEG®* ZIEXTENZO®*	1 injection de 6mg SC / cycle de chimiothérapie 24h-72h après la fin de la chimiothérapie		Produit sur des cellules d'*Escherichia coli* par la technique de l'ADN recombinant suivie d'une conjugaison au polyéthylèneglycol (PEG)
(Lipegfilgrastim)§				

*rHu : recombinant humain - * indique un produit biosimilaire - § Non commercialisé en France*
Tableau 10 – Différents FCH disponibles en France.

2. Prophylaxie primaire par FCH

L'indication des FCH est basée sur l'estimation du risque de neutropénie fébrile exprimé en pourcentage.

Si le risque est supérieur à 20%, et s'il n'existe pas d'autre alternative de chimiothérapie aussi efficace mais moins risquée, l'administration prophylactique est recommandée (30,36). A l'inverse, si le risque est inférieur à 10%, les G-CSF ne sont pas recommandés.

Dans les protocoles pour lesquels le risque est compris entre 10 et 20%, la prescription est pondérée par la présence de facteurs de risque de neutropénie fébrile. Pour plus de simplicité, l'EORTC propose un arbre décisionnel pratique (cf. **Figure 1** et **Tableau 11**) repris par les recommandations MASCC/ESMO (33). Il faut également prendre en compte l'existence d'une situation infectieuse à risque (chirurgie récente, infection patente…) ainsi que les ATCD personels de chimio et/ou radiothérapie (qui sont particulièrement à risque de neutropénie) et qui pourront bénéficier d'une prophtlaxie primaire par FCH. Une étude est en cours dans cette situation à risque intermédiaire pour tenter d'identifier plus clairement les facteurs prédicitifs dans la vie réelle (37).

Il est intéressant de noter que le risque de neutropénie fébrile survient avant tout à la première cure (33,38), ce qui plaide pour l'utilisation des FCH en prophylaxie primaire (lorsque le risque de neutropénie le justifie), dès la première cure, notamment pour les cancers bronchiques à petites cellules (dans lesquels le risque d'envahissement médullaire est plus important).

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