CHIMIOTHERAPIE, THERAPIES CIBLEES ET IMMUNOTHERAPIE

1. Existe-il des différences d'efficacité des traitements systémiques du cancer broncho-pulmonaire sur les métastases osseuses ?

1.1 Chimiothérapie.

Aucune donnée solide ne plaide pour une différence d'efficacité des molécules actuelles de chimiothérapie sur les métastases osseuses des cancers bronchiques. Ainsi, la présence de métastases osseuses ne conditionne pas directement le choix des molécules de chimiothérapie.

1.2 Thérapies ciblées.

Le démembrement moléculaire des CBNPC de stade IV a permis d'enrichir les possibilités thérapeutiques par l'utilisation des thérapies ciblées (TKI, anti-ALK). Il semble exister en revanche une relation intéressante entre la réponse des métastases osseuses et les inhibiteurs de l'EGFR (erlotinib, gefitinib). Des cas de meilleur contrôle de la douleur, de réponse osseuse prolongée et de retard à la survenue d'une complication osseuse ont été rapportés (35,36). Ces données sont également corroborées par des travaux *in vitro* et *in vivo* qui suggèrent l'implication de la voie de l'EGFR dans le cercle vicieux de la résorption osseuse induite par les métastases osseuses (37). Les mécanismes sont complexes mais peuvent se résumer en une inhibition de la production de facteurs ostéolytiques et de la prolifération des ostéoblastes, et un blocage de la différentiation des ostéoclastes par la voie RANK-RANKL. Cette action particulière des inhibiteurs de l'EGFR sur le site osseux est illustrée par le « *bone flare* » qui est fréquemment rapporté sous thérapie ciblée et qui correspond à une réponse carcinologique (34). L'ensemble de ces données explique l'amélioration des symptômes osseux souvent rapportés dans les séries comportant des patients avec métastases osseuses sous TKI. Dans une étude rétrospective, la combinaison d'un anti-EGFR et d'un bisphoshonate s'accompagne de moins d'évènements osseux (SRE) et d'une amélioration de la survie PFS mais pas en survie globale (38). Enfin, dans une petite série rétrospective (39) 82 patients métastatiques mutés EGFR, l'existence de localisations osseuses ne semble pas modifier la PFS sous TKI-en première ligne.

1.3 Immunothérapies

La première publication concernant l'efficacité de l'immunothérapie sur le site métastatique osseux était l'analyse rétrospective de Tamiya *et al.* Elle ne montrait pas de différence d'efficacité (survie sans progression) dans le sous-groupe de patients atteints de métastases osseuses (n=66) par rapport à ceux sans métastases osseuses (n=135) (p=0.192) mais la survie médiane sans progression dans cette population était très courte (de l'ordre de 3 mois) (40). L'étude de Schmid *et al.* n'a porté que sur un nombre très restreint de patients (n=52 dont 16 métastastiques osseux) mais suggérait qu'il pourrait y avoir des réponses différentes suivants les sites métastatiques. Cette étude était rétrospective, basée sur la relecture de scanner selon les critères RECIST mais ne précisait pas les critères d'analyse de l'os. Elle suggérait une moindre réponse des lésions osseuses (41). L'analyse de Facchinetti *et al.* a également regardé les paramètres biologiques, cliniques et d'extension prédictifs de la survie. En univarié, les courbes pourraient être moins bonnes en cas de métastases osseuses mais cela n'est pas significatif et ce critère n'a pas été retenu dans l'analyse multivariée (42). L'étude Checkmate 227 de phase III sur les CBNPC métastatiques, récemment publiée, prévoyait une randomisation différente selon le statut PDL1 du patient. Les patients avec un PDL1 ≥ 1% étaient randomisés entre une combo-immunothérapie (ipilimumab + nivolumab), une mono-immunothérapie (nivolumab) et une chimiothérapie à base de sels de platine. L'étude a montré une supériorité de la combothérapie sur la chimiothérapie en termes de survie globale chez les PDL1 ≥ 1% (co-objectif principal). Le bénéfice sur la survie était observé que les patients soient (n=208) ou non (n=585) métastatiques osseux (43). Il n'existe donc pas à ce jour de critères limitant l'utilisation de l'immunothérapie chez les patients porteurs de métastases osseuses.

2. Doit-on tenir compte de l'importance de l'extension osseuse pour le choix du traitement et l'adaptation des doses ?

Dans les cancers bronchiques, les métastases osseuses sont souvent multiples d'emblée avec en moyenne 3 sites osseux atteints (44). Elles surviennent en général dans l'évolution de la maladie (60%). L'importance de l'extension osseuse ne conditionne pas le choix des molécules de chimiothérapie ni leur dose. En revanche la vigilance est requise sur la néphrotoxicité cumulative que peut représenter l'utilisation des sels de platine, du pemetrexed utilisé de surcroît en maintenance et des biphosphonates (contre-indication si le DFG est inférieur à 30 ml/mn). En cas de clairance de la créatinine abaissée il est conseillé alors de baisser les doses de chimiothérapie et souvent d'arrêter le biphosphonate. L'administration de dénosumab n'est pas limitée par le débit de filtration glomérulaire. Les TKI ne nécessitent pas d'adaptation de dose en cas d'insuffisance rénale faible à modérée mais sont déconseillés en cas d'insuffisance rénale sévère.
Enfin, le traitement systémique que représente la chimiothérapie, les thérapies ciblées et l'immunothérapie, ne doit en aucun cas être un obstacle à la réalisation d'une technique interventionnelle qui serait nécessaire et prioritaire en cas de menace fonctionnelle immédiate. On sera alors vigilant pour la période du Nadir. L'importance de l'extension osseuse et ses complications conditionne la stratégie globale de prise en charge des métastases osseuses par la hiérarchisation des traitements dans laquelle le traitement systémique s'inscrit.

Recommandations

-Il n'y pas d'argument pour une différence d'efficacité des protocoles actuels de chimiothérapie ou les thérapies ciblées sur les métastases osseuses des cancers bronchiques.
- Les données actuelles avec l'immunothérapie sont insuffisantes.
-L'importance de l'extension osseuse et ses complications conditionne l'imbrication des différents traitements dans laquelle s'inscrit le traitement anti-tumoral.
-Une attention particulière doit être portée en cas d'utilisation concomitante des sels de platine, du pemetrexed et des biphosphonates en raison d'une néphrotoxicité cumulative.
-Le phénomène de « *bone flare* » traduisant un blocage tumoral rapide et un allumage de la formation osseuse, est particulièrement fréquent sous anti-EGFR et ne doit pas conduire à l'arrêt du traitement.

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