MultipleMyelomaHub

Patients eligible for transplant, Patients non-eligible for transplant, Relapsed/refractory patients, General MM

Hexokinase-2 expression is linked to false-negatives in FDG-PET imaging of MM patients

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For both the diagnosis and assessment of Multiple Myeloma (MM) progression, 18F-Fluorodeoxyglucose (FDG) positron emission tomography (PET) is routinely used, along with diffusion-weighted magnetic resonance imaging with background signal suppression (DWIBS). Both rely on exclusive properties of tumor cells compared with normal cells to detect tumor deposits and bone lesions: FDG-PET relies on increased glucose uptake and DWIBS relies on differences in water diffusion to detect changes in tissue architecture. However, discrepancies between the two methods have been observed, such that some patients with advanced disease as assessed by DWIBS were reported to be disease-free when assessed by FDG-PET – so-called 'false negatives'.

This phenomenon was investigated by Leo Rasche and Edgardo Angtuaco from The University of Arkansas for Medical Sciences, Little Rock, AR, USA, along with collaborators from five other institutes, and their results were published in Blood in April 2017. In their study, 227 patients with newly diagnosed MM, that were transplant-eligible, were assessed simultaneously with FDG-PET and DWIBS, and additionally characterized using fluorescence in situ hybridization (FISH) and gene expression profiling (GEP).

Key Findings:

- FDG-PET was performed on a Biograph, Reveal or Discovery scanner; DWIBS was performed on a 1.5 Tesla Philips Achieva scanner
- Patients (pts) were categorized as follows:
  - $DWIBS^{pos}PET^{pos}$ = disease detected by both methods
  - $DWIBS^{pos}PET^{neg}$ = disease detected by DWIBS only
  - $DWIBS^{neg}PET^{neg}$ = disease not detected by either method
  - No DWIBS-negative and FDG-PET-positive pts were found
- Out of 227 pts, the proportion in each category was:
  - $DWIBS^{pos}PET^{pos}$ = 186 (81.9%)
  - $DWIBS^{pos}PET^{neg}$ = 26 (11%) - 5 pts had focal lesions (FLs) only, 13 had both FLs & diffuse involvement, and 13 had extensive diffuse involvement; none were assigned to the HY (P<0.0001) or PR (P=0.01) UAMS molecular subgroups
  - $DWIBS^{neg}PET^{neg}$ = 15 (6.6%) - significantly less adverse chromosomal prognostic markers and a trend for a lower tumor burden; may fall below detection threshold
- GEP identified 21 genes differentially expressed between $DWIBS^{pos}PET^{pos}$ and $DWIBS^{pos}PET^{neg}$

- Most common gene with differential expression = Hexokinase-2 (*HK2)* – which catalyzes the first step of glycolysis, and was 5.3x lower in PET-negative cases (P<0.001)
- Other differentially expressed genes: up-regulated = *DDR1*, *MPZL3*, *NDRG2*, *TMBIM6*; downregulated = *NPM1*
- *HK2* has been associated with FDG uptake in mouse models; low *HK2* expression leads to decreased levels of metabolically trapped FDG in tumor cells
- *HK2* expression was significantly increased in the HY molecular subgroup, corresponding to the lack of $DWIBS^{pos}PET^{neg}$ cases in this subgroup
- *HK2* expression positively correlated with proliferation (Spearman's rank correlation rho=0.24, P<0.001) but some cases had low *HK2* expression and increased proliferation rates, excluding proliferation as a parameter solely explaining low *HK2* expression in PET-false negative patients
- Analysis of copy number arrays (CNA) and the *HK2* common polymorphism rs923273 did not explain mechanistic details underlying low *HK2* expression

The discrepancy between 11% of the MM patients tested that had positive results for DWIBS but were negative when assessed by FDG-PET, were linked to lower levels of hexokinase-2, which affects processing of the FDG tracer. Clinicians should be mindful of this and where possible use multiple modes of assessment; new PET tracers may also help to eliminate such false negatives. Larger studies are required to elucidate the mechanism of such a phenomenon, as well as any prognostic significance.

References

1. Rasche L. and Angtuaco E. *et al.* Low expression of hexokinase-2 is associated with false-negative FDG-positron emission tomography in multiple myeloma. Blood. 2017 Apr 21. pii: blood-2017-03-774422. DOI: 10.1182/blood-2017-03-774422. [Epub ahead of print]