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EDITORIAL

Molecular imaging with FLT: a case of Cassandra's curse?

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In Homer's classic tale of the downfall of Troy, names like Paris, Helen, and Achilles are widely recognized as tragic figures but perhaps the saddest character is Cassandra, the daughter of Troy's king, Priam, and the sister of its greatest hero, Hector. Cassandra was a priestess given the gift of prophesy by Apollo, but then, after rejecting the god's amorous advances, cursed by him to not be believed. While regulatory authorities, and many clinicians, are obsessed with the ability of imaging to find sites of disease, the ability to predict future events, which we call prognostication rather than prophecy, is largely ignored. As such, molecular imaging, in general, seems to have suffered as Cassandra did.

When the PET tracer FLT was first described [1], there was great excitement that it would overcome one of the major limitations of FDG by not being subject to false positive results related to inflammatory processes. In canine imaging studies, there was uptake almost exclusively in the bone marrow. However, in a preliminary human evaluation in this seminal paper, it was noted that while there was high uptake in a lung cancer, as well as in the bone marrow, there was also high uptake in the liver, suggesting altered handling of this tracer by the human liver compared to that in the dog. The authors pointed out the possibility that this would limit detection of metastases in these tissues that represent amongst the most common sites of cancer dissemination. This biodistribution was to largely spell the doom of this tracer as a diagnostic agent. Although FLT was able to detect one of the relatively rare aggressive cancers to lack significant FDG-avidity, diffuse gastric cancer [2], the inability of complement staging information has been a limitation. A further issue for the tracer has been uptake in active germinal centres of reactive lymph nodes [3]. An exception to the general superiority of FDG in detecting disease has been in identifying brain metastases and high-grade primary brain neoplasms, based primarily on the very low background activity of FLT in normal brain tissue. However, C-11 methionine and F-18 fluoro-ethyl-tyrosine (FET) may perform as well or better by detecting disease based on amino-acid transport into varying grades of tumour [4] and because its uptake is not impaired by an intact blood brain barrier [5]. Nevertheless, preliminary data supported the utility of FLT in grading of gliomas, which is an important prognostic indicator [6, 7].

Although increased cellular proliferation is one of the hallmarks of cancer, not all cancers have high rates of growth, despite having metastatic potential. Neuroendocrine neoplasia (NEN) is a case in point wherein the majority of metastatic cases are still low-grade, as assessed by a tissue biomarker of proliferation, Ki-67. While most NEN patients have G1 disease characterized by a Ki-67 < 3%, even in a population of NEN patients with predominantly G2 or G3 disease, FLT was positive in only 37% of cases [8]. Accordingly, its role in detecting sites of disease is compromised in an era when somatostatin receptor imaging, combined with FDG PET/CT for higher-grade NEN, has become a routine part of the diagnostic paradigm, at least in some parts of the world [9]. Similarly, in metastatic phaeochromocytoma/paraganglioma, FLT uptake was minimal in even progressive lesions compared to FDG [10].

Nevertheless, cellular proliferation is clearly important prognostically and the ability to suppress proliferation is likely to prolong progression-free survival and, in highly aggressive tumours, this may impact overall survival. At initial staging, diseases that have heterogeneity in proliferation may benefit from prognostic stratification based on cellular proliferation. An obvious scenario is follicular lymphoma (FL), which not only has various grades but also is prone to transformation to aggressive lymphoma, particularly diffuse large B-cell lymphoma (DLBCL). The latter has been shown to be positive on FLT PET with higher SUV being an adverse prognostic indicator for response to the R-CHOP treatment regimen [11]. However, higher uptake of FDG fills a similar role in detecting transformed lymphoma and

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FDG PET/CT now widely used for both the staging and response assessment of lymphoma [12]. A comparison of FDG and FLT in 114 patients demonstrated that there was a more marked difference in SUVmax between DLBCL and FL with FDG than with FLT [13]. Following treatment of lymphoma, residual masses are relatively common. An early comparison of FLT and FDG demonstrated that lack of uptake on either was associated with longer median overall and progression-free survival but failed to indicate a benefit of FLT over FDG in this clinical setting [14].

Despite these somewhat discouraging results, in a study involving 54 patients with DLBCL, an evaluation of the change in FLT uptake, based on either SUVmax or SUVmean between a baseline scan and another done in the first week of R-CHOP, was greater in patients who subsequently achieved a complete response than those who didn't and was also predictive of survival [15]. Similar results were found in a study involving 61 patients with DLBCL treated with R-CHOP, in which SUVmax after one cycle of treatment was predictive of 5-year overall survival and better able to stratify prognosis than FLT findings at either baseline or the end of treatment [16]. A further study in 65 DLBCL patients using FLT PET/CT after 1–2 cycles of R-CHOP supported the ability to predict both progress-free survival (PFS) and overall survival (OS) [17]. However, in this study wherein 4 cycles of R-CHOP were followed by a relatively aggressive consolidation regimen of 3 cycles of ICE chemotherapy, the positive predictive value of an early scan was considered by the authors to be insufficient to warrant even more aggressive treatment intensification.

These prior studies provide useful background to assessing the significance of a recent study in the *European Journal of Nuclear Medicine and Molecular Imaging*, which has provided further support for the use of FLT PET/CT in monitoring response [18]. In this prospective trial involving 92 patients with DLBCL treated with either of two standard chemotherapy regimens combined with rituximab, all cases were evaluated after 2 cycles of treatment by both interim FDG PET/CT (iFDG) and FLT PET/CT (iFLT). Due to logistic and funding constraints, no baseline FLT was acquired and therefore the primary analysis of FLT was based on visual assessment with positive lesions being confirmed by demonstration of a higher SUVmax in detected lesions than the SUVmean in left atrial blood pool. There are few data to indicate whether these are the appropriate interpretation criteria for FLT PET. A visual scoring system based on comparison to normal organ uptake, somewhat similar to that used for the Deauville score (DS), has been proposed for assessing malignancy in lung lesions [19], but this has not been validated in lymphoma. Neither has an absolute SUV been defined for defining a positive scan. Therefore, the simplicity of the assessment criteria used in this trial is somewhat appealing for translation into the clinical setting and the lack of requirement for an additional baseline scan would potentially allow substitution for iFDG, which is now widely integrated into response evaluation. The primary rationale for this in aggressive lymphoma is to identify patients in whom treatment might need to be escalated to diminish treatment failure rates and thereby improve survival.

The case for substitution of iFDG by iFLT is potentially supported by the finding by Miamimoto and co-workers that a substantially higher proportion of patients were negative after 2 cycles of treatment (73% versus 58%), and the relapse rate in the patients with a positive iFLT was substantially greater than in those with a positive iFDG based on DS (56% versus 30.8%). Further, they found that the PFS in iFLT negative patients was statistically significantly longer than in those with a positive iFLT, whereas this was not the case for iFDG positive patients. On multivariate analysis that included various analysis methods of FDG response, only iFLT was predictive of 3- and 5-year PFS. Together, these data suggest that less patients would need to be considered candidates for treatment escalation, but for those that are positive on iFLT, the adverse prognostic implications of the scan would provide a stronger incentive to potentially increase the toxicity of treatment in order to reduce the likelihood of treatment failure.

Like Cassandra, iFLT PET/CT seems to predict the future but whether the information will be heeded and used to avoid tragic outcomes by translation into the clinic remains in the hands of the gods!

Declarations

Ethics approval Institutional Review Board approval was not required because the paper is an Editorial.

Informed consent Not applicable.

Conflict of interest The author declares no conflicts of interest relevant to this article.

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