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The Role of 18F-FDG PET CT in Monitoring Tumour Response

Early evaluation of tumour response to chemotherapy is crucial for optimal management of oncology patients, especially given the lack of suitable response evaluation criteria to new molecular-targeted anticancer therapies. 18F-FDG PET-CT offers an added value for assessing aggregate (dimensional and metabolic) tumour response after completion of treatment in various cancer types. This methodology is being currently investigated to follow tumour responsiveness sequentially, after one or more courses of chemotherapy.

In fact, correlation between early changes in 18F-FDG uptake and overall patient survival represents a very meaningful research opportunity. The preliminary results call for systematic inclusion of 18F-FDG PET technology early in the therapeutic algorithm. To properly place 18F-FDG PET in treatment timelines (on both cancer-type-basis and regimen- basis) will change current therapeutic concepts leading to individualise treatment of patients. Patient management might be changed. For instance, in non responder patients this novel diagnostic approach would hamper useless "wait and watch" attitude in implementing further options or identifying those needing additional therapeutic strategies. On the other hand, for those patients revealing promptly a favourable metabolic response a cost-sparing approach could be implemented avoiding expensive diagnostic procedures during the follow-up as well as the risk of over-treating. In any case, since even a partial metabolic response may be an indication for continuing therapy, the advantage of metabolic assessment over conventional procedures may be clinically relevant.

18F-FDG PET has a consolidating role when therapy efficacy is assessed after completion of treatment regimens in terms of both outcome and timing in performing PET scan. In order to attain the highest sensitivity for the detection of residual tumour cells 18F-FDG PET should be performed as late as possible after completion of therapy. However, a deferral of three to six weeks seems to be a realistic compromise.

European Recommendations

The European Organisation for Research and Treatment of Cancer (EORTC) PET study group has formulated some recommendations in order to properly implement such methodology (Young 1999). In particular, it has been suggested to execute pre-treatment and post-treatment scans for comparison, to acquire pre-treatment scans as close as possible to the commencement of treatment and to adapt the timing of the post-treatment scans to the chosen endpoint, being it sub-clinical or clinical, and to the chemo-responsiveness of the tumour type.

In some tumours attempts to estimate the capabilities of 18F-FDG PET earlier (few weeks) after completion of treatment have been made, but needs to be confirmed in larger series. The clinical impact of 18F-FDG PET has also been evaluated at midtherapy. Nevertheless, this latter approach seems to be reliable only for some settings and cannot be implemented routinely. On the other hand, there is at the present sufficient evidence (Avril and Weber 2005; Brun et al. 2002; Wahl et al. 1993; Weber et al. 2001; Weber et al. 2003; Wieder et al. 2004) that the early assessment of tumour response to therapy by 18F-FDG PET may play a crucial role in patient management.

Current data endorse to consider one to three weeks after initiation of first chemotherapy cycle the optimal time in performing PET scan if an early tumour response assessment is required (see figure 1, p. 34).

This approach appears to be suitable for many solid tumours and therapeutic regimens, and could be implemented in neo-adjuvant and adjuvant settings as well as during the treatment of metastatic disease. In addition, a similar trend has been reported in studies on lymphomas (Kostakoglu et al. 2002; Spaepen et al. 2001). The early identification of chemotherapy-refractory lymphoma patients provides a basis for alternative therapeutic strategies recognising those who would benefit from more intensive treatment programmes.

It should be highlighted that the present definition of tumour response is based on the measurement of changes in tumour size as determined with morphological imaging methods (RECIST version 1.0 and 1.1) (Eisenhauer et al. 2009; Therasse et al. 2000). However, morphological imaging have limitations in assessing the therapeutic effect since changes in tumour size ensue the biologic response to therapy, which is considered a trouble in early response monitoring. Accordingly, RECIST criteria have been recently updated revising, for instance, the concepts of target and non-target lesion as well as the approach to the assessment of lymph nodes (Eisenhauer et al. 2009) and indicating that it is sometimes reasonable to incorporate the use of FDGPET scanning (particularly for possible 'new' disease). Lately, a draft framework for PET response criteria in solid tumours has been proposed (PERCIST 1.0) (Wahl et al. 2009).

Early Use Proven to be Superior

In addition, the introduction of molecular-targeted agents such as the angiogenesis inhibitors, requires new alternative end points for monitoring therapeutic effects since they determine biological effects other than cytotoxicity. This context has necessitated new imaging modalities.

The use of 18F-FDG PET early in the course of therapy is supported by two main evidence; the registered high accuracy for predicting tumour response and patient outcome and the capability to assess molecular mechanisms involved in the process.

The uptake threshold settled for identifying response depends on multiple variables such as tumour type, type of therapy and interval after onset of therapy. However, a mean reduction in 18F-FDG standardised uptake value (SUV) with effective chemotherapy has been detected for responding patients across tumour types and chemotherapeutic regimens (Findlay et al. 1996; Haberkorn et al. 1993; Wahl et al. 1993). A decrease of 10-35 percent was seen in the SUVBW (body weighted) value after one cycle of chemotherapy in responders. This threshold increased to 40-50 percent after three cycles or at the end of treatment. Generally, a 35 percent cut-off after one cycle of therapy appears to be a reliable predictor of response throughout different cancers leading to sensitivities, for predicting therapy response, higher than 70 percent.

Closer Molecular Assessment Essential

In terms of clinical response, a reduction of greater than 25 percent was seen at some time points in the treatment of responding tumours. None of the studies reported a significant reduction in 18F-FDG uptake in non-responding tumours. It should be underlined that 18F-FDG PET, for its intrinsic characteristics, allows a molecular assessment, which is essential to understand the mechanisms sustaining the therapeutic response. For instance, it has been helpful in detecting changes in glucose metabolism, which reflect predominantly the cytotoxic effects and thus the loss of viable cells after effective radiotherapy (RT). In addition, it is able to reveal the acute effects of chemotherapy on cellular metabolism which are attributable to rapid apoptotic cell death rather than to a direct cytotoxic effect (Spaepen et al. 2001).

In spite of this, results from 18F-FDG PET imaging may be associated with high false positive findings due to tissue damage or with false negative results because of alterations in tracer kinetics, mainly after RT. For instance, radiotherapy may cause an inflammatory response and 18F-FDG uptake associated with activated macrophages and neutrophils may confuse signal interpretation. In addition, during the first hours after the treatment a transient "flare phenomenon" has been described (De Witte et al. 1994). It would be a further confusing factor in studies expressly designed to detect reduction in tumour's 18F-FDG uptake. Nevertheless, this early "flare phenomenon" may have prognostic significance. Although there is no uncertainty regarding the evidence that radiation-induced inflammation accumulates 18F-FDG, its amount is often significantly lower than in untreated tumours. As a result, it appears that the negative effect of radiation-induced inflammation on correct evaluation of tumour response by 18F-FDG PET might not be so critical.

Early Evaluation May Generate False Negatives

Early evaluation at one month after the completion of RT may also generate false-negative results. Immediately after RT, the incorporation of 18F-FDG into tumour cells may decrease in spite of tumour viability. It was hypothesised that the radiation-induced changes in 18F-FDG uptake might be determined from altered cellular glucose transport mechanisms related to GLUT-1, hexokinase, or vascular damage rather than cell death (Higashi et al. 2000).

Recently, PET-CT technology has showed to convey significant benefit in tumour staging as compared to PET or CT alone. It has enhanced anatomic localisations of anomalies detected by PET alone replacing it in the evaluation of cancer patients. This methodology has not been extensively implemented for assessing tumour response after treatment so far. Although the lack of standardised criteria, its role for the aggregate analysis of metabolic and morphologic changes induced by treatment in cancer is growing.

Conclusions

18F-FDG PET/CT has already a well-established role in the diagnosis and staging of a wide variety of solid cancers. Preliminary data demonstrate it can also provide early information on tumour response to therapy. In addition, an expanding range of radiotracers is currently being investigated for monitoring response before, during or after therapeutic interventions including radiotracers of DNA synthesis and agents for imaging amino acids, hypoxia and tumour expression of receptors.

As anticancer therapy becomes more individualised, it is increasingly important to identify response to treatment as early as possible. Early identification of responders and non-responders may allow physicians to optimise treatment and to spare costs and morbidity in these patients.

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