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EDITORIAL

The "reset button" revisited: why high activity ^{131}I therapy of advanced differentiated thyroid cancer after dosimetry is advantageous for patients

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The treatment of advanced differentiated thyroid cancer (DTC) remains challenging. In spite of our best efforts, about 15% of patients with high-risk DTC have a significantly reduced life expectancy as many do not respond sufficiently to ^{131}I therapy to prevent recurrence and progression of DTC, or even death [1]. Furthermore, it has been firmly established that the more advanced the DTC, the worse will be the prognosis [1]. Therefore, there is an ongoing quest to optimize ^{131}I therapy in patients with locally advanced or metastatic disease. Although at the other end of the disease spectrum, the discussion on optimization of ^{131}I therapy in advanced DTC essentially comes down to the same point as is currently debated extensively in low-risk and intermediate-risk DTC: what ^{131}I activity is "best" or "better" [2–4]? However, in contrast to the discussion in patients at the lower end of the risk spectrum, in patients with advanced DTC, the scientific debate is not about a "low", a "lower" or "no" ^{131}I activity, but instead about a "high" or a "higher" ^{131}I activity [5, 6].

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For advanced DTC several ^{131}I activity selection strategies are available [7–11]. The most commonly used approach is empirical activity selection, in which the physician chooses an activity based on convention, experience and patient-related parameters. With this strategy patients with advanced DTC are most commonly given activities of 3,700, 5,550 or 7,400 MBq [12], with some physicians going as high as 11,100 MBq. However, it has been demonstrated clearly, not just for ^{131}I therapy but for essentially all therapy procedures with radiopharmaceuticals, that absorbed doses delivered to lesions per unit of administered activity can range widely [13, 14]. It is therefore quite feasible that, while for a given patient a specific administered activity may deliver a high lesion absorbed dose, a second patient may receive a much lower lesion absorbed dose from the same or even higher activity. The second available strategy is to perform lesion dosimetry. In this case, the activity to be administered is determined after a pretherapeutic dosimetric assessment (either with ^{124}I or ^{131}I) to calculate the minimal activity required to achieve an effective absorbed dose [13–15]. This strategy primarily aims to deliver effective ^{131}I therapy with an activity as low as reasonably achievable (ALARA). The third strategy is to determine the therapeutic activity needed to deliver a blood/bone marrow absorbed dose of 2 Gy based on blood and whole-body measurements [5, 6, 16–19]. This 2 Gy limit is a commonly accepted value based on the findings of Benua et al. [18] and is used with the aim of minimizing haematological complications after ^{131}I therapy. The primary aim of this strategy is to give an activity which is as high as safely achievable (AHASA). The underlying rationale for an AHASA approach is based on the hypotheses that higher administered activities result in higher absorbed doses delivered to lesions and that treatment outcome is related to the level of absorbed dose delivered. The AHASA approach has been endorsed by the European Association of Nuclear Medicine in its procedural guidelines [17].

Although any comparative study in DTC is difficult because of, among other things, the long observational periods required to get reliable data on long-term outcomes, such studies are all the more difficult in advanced DTC because fortunately it only affects a small fraction of the total DTC patient population. The debate in relation to lower risk DTC patients is already difficult because of the limited (but growing) number of long-term observational and shorter term prospective comparative studies. Until recently, only a few single-centre observational studies with encouraging results were available in advanced DTC. Such studies showed dramatic reductions in thyroglobulin (Tg) levels of 97–99% in a considerable proportion of patients treated with an AHASA activity [16]. However, the lack of data comparing different activity selection strategies in relation to outcome has made the debate in advanced DTC almost impossible. This situation is now slowly changing. In the last few years two larger studies comparing patient cohorts with advanced DTC treated with a fixed activity of either 3,700 MBq or 7,400 MBq, or a (higher) activity given after blood/bone marrow dosimetry have been published [5, 6].

Both these studies unfortunately failed to show a statistically significant survival benefit for the entire group of patients with advanced DTC who were treated with an AHASA activity over those treated with a fixed activity. A study by Klubo-Gwiezdzinska et al. [5] showed a tendency for better long-term disease-specific survival in patients receiving AHASA therapy, and also showed a significant difference in favour of AHASA in patients with locally advanced disease only. In contrast, a study by Deandreis et al. [6] showed a tendency for a worse survival in in patients receiving AHASA therapy. Whereas the study by Klubo-Gwiezdzinska et al. demonstrated some benefits in terms of a significantly better outcome on measures such as the rate of complete remission after a single course of therapy [5], the study Deandreis et al. failed to show this effect [6]. Deandreis et al. concluded that the lack of apparent benefit from AHASA activities made the value of dosimetrically determined AHASA activities questionable. In other words, the AHASA therapy strategy led to the same outcome in patients in a worse clinical condition as in patients with less advanced disease.

Do these studies now spell the end of blood/bone marrow dosimetry based AHASA activities? Perhaps not. It might even precisely be the lack of a significant difference between the AHASA and the fixed activity groups that proves the worth and efficacy of the AHASA strategy.

Inherent to any retrospective investigation is the risk of selection bias. When retrospectively comparing two treatment regimens, consideration needs to be given to the fact that patients are allocated to a specific treatment based mainly on the severity of disease. In the studies by Klubo-Gwiezdzinska et al. [5] and Deandreis et al. [6] such a selection bias was present in the former, and even had a major effect on the results in the latter. It is precisely those patients who are sicker who get allocated to dosimetrically determined activities. Whereas in the study by Klubo-Gwiezdzinska et al. [5] this bias was comparatively minor and mostly concerned a higher frequency of local tumour invasion in those who were treated with an AHASA activity, the differences in the study by Deandreis et al. [6] are much more serious. In this analysis the patients treated with dosimetry were much older (a median of 10 years) and had a much greater extent of distant metastatic disease. Each of these factors separately would be sufficient to cause a significant difference in DTC-specific survival in favour of the fixed activity group, let alone the combination of the two. And yet, no such difference was found.

A possible explanation for the lack of a significant difference in prognosis, or even marginally better results in terms of outcome, in spite of a considerable bias against the AHASA activity group, is of course the efficacy of AHASA ^{131}I therapy. The effect seen here has to be considered analogous to the situation in initial postoperative ^{131}I treatment. In this case it has been shown that complete remission after the first ^{131}I therapy in high-risk patients effectively functions as a “reset button” and reduces the risk of DTC recurrence and tumour-related death to the risk level in those who are considered “low risk” at initial treatment [20]. Similarly, it can be argued that AHASA therapy is a successful therapy in that it reduces the risk of DTC-related death in the very highest risk patients to the level in patients at a considerably lower risk level.

Furthermore, the aim of blood and bone marrow dosimetry for ^{131}I therapy is ensure that higher levels of activity can be administered safely. As such, comparisons with fixed activity schedules should also examine whether there is greater toxicity with the AHASA approach. No such increased toxicity was found by Deandreis et al. [6], indicating the safety of the AHASA approach, as also reported by other authors [16, 21]. Of course, this interpretation of the data is not without controversy – a lack of a difference by definition does not constitute definitive proof of efficacy. However, when baseline conditions between two groups differ significantly, the lack of a significant difference also cannot be interpreted as proof of a lack of efficacy (as was done by Deandreis et al. [6]).

While we consider that the study by Klubo-Gwiezdzinska provides an initial indication in favour of AHASA, Lee et al. found that 45% of patients who failed to respond to pretreatment with a fixed activity approach, achieved a partial or complete radiological response after ASAHA therapy [22]. Though at a low level of evidence, it nonetheless seems that there are at least two papers supporting the advantages of AHASA.

The controversy in the interpretation of the available material again illustrates the need for prospective, randomized, controlled studies comparing dosimetry-based ^{131}I therapy and conventional fixed-activity based strategies to elucidate the benefits of AHASA therapy with regard to patient-relevant

outcome measures. These should preferably be done in combination with lesion dosimetry in order to better assess parameters affecting treatment success such as the lesion absorbed dose. Notwithstanding the need for such studies and until results are available, the authors advocate that the available evidence is viewed in a light more favourable to AHASA ^{131}I therapy. The current evidence appears to show that in patients with advanced DTC, dosimetry-based high-activity ^{131}I therapy seems more effective in improving minor outcome markers and survival in at least a subgroup of patients. Furthermore, the treatment can improve the expected mortality rate in patients with a clearly higher baseline risk of DTC-related death. Therefore, we advocate that an AHASA-based ^{131}I activity approach is considered in the treatment of patients with advanced DTC after pretherapeutic dosimetry in accordance with the relevant EANM procedure guidelines [17].

Compliance with ethical standards

Conflicts of interest F.A.V. was a consultant to Bayer Healthcare and SanofiGenzyme and has received speaker honoraria from Diasorin and SanofiGenzyme. M.L. was a consultant for AstraZeneca, Bayer Healthcare, Eisai, Ipsen, Novartis, SanofiGenzyme and Sobi, and has received speaker honoraria and research support from SanofiGenzyme and Henning. L.G., M.L., C.C., N.C. and G.F. declare no potential conflicts of interest.

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