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A structured approach to uncommon cancers: what should a clinician do?

In this issue of *Annals of Oncology*, Pecuchet et al. [1] have produced an elegant, original paper describing an innovative approach to the management of metastatic collecting duct carcinoma, using bevacizumab, gemcitabine and a platinum complex. They have shown surprising anticancer activity, which appears to have been sustained. They have addressed the usual concerns about case selection bias, positive response bias and pathology review of an uncommon tumor, and thus, this regimen certainly will bear confirmatory testing in other structured trials, especially as this triplet really does seem to give a different result from the more conventional gemcitabine–cisplatin combination or the established MVAC regimen (notwithstanding the absence of level 1 data at this time).

The editorial review of this manuscript raised an important generic question, viz. what should a clinician do when approaching a patient with a truly uncommon or rare tumor? Using a cut-off figure of 15 new cases/100 000 of population per year as a definition for 'rare cancers', Greenlee et al. [2] have suggested that these tumors cumulatively account for around 25% of incident cases in the United States. This figure seems inflated to me, because of their cut-off value, especially as I do not view testicular cancer as a rare tumor (yet it has an incidence of 6.8/100 000 males per year). Nonetheless, Greenlee et al. make an important point—rare tumors cumulatively do constitute a significant proportion of the total cancers presenting, yet we have remarkably little information available to guide management, when compared with the common tumors that arise in breast, lung, prostate, colon, pancreas and bladder. A similar situation appears to apply to oncology practice in Europe, in a report using a cut-off of less than six new cases/100 000 of population per year, with the accompanying suggestion that outcomes are worse for the patients with rare tumors [3]. Of importance, there is masking of some rare situations—large population surveys do not address the problems presented by rare subtypes of common malignancies (e.g. small-cell prostate cancer, collecting duct carcinoma of kidney and many others), and the literature often fails to address atypical consequences of malignancy, such as the gene-associated endocrine syndromes [4].

Because of the rarity of many of these groups of cases, there is remarkably little useful information available to the clinician regarding optimal approaches to diagnosis and management. As a result, it has been suggested that there should be more publication of small case series or even isolated case reports, a view with which I strongly disagree—unvalidated anecdotes without pathology and staging review and adequate follow-up will provide little useful information to provide a reliable guide to appropriate and optimal care for these patients, and is likely to be heavily influenced by the recent trend towards open-access publication.

Equally important, one should not forget the needs of patients and their families, when faced with these rare tumors—it is much more challenging for them to secure the information that they need, and this adds to their anxiety and fear, especially when the oncologist indicates lack of certainty and/or experience with the specific condition. Unfortunately, in their anxiety, such patients will often turn to the internet, and unquestioningly be guided by advertorials or anecdotes that are dominated by rhetoric rather than fact.

Attempts have been made to help with the problem by producing two definitive texts—four editions of Textbook of Uncommon Cancer [5] and the French language publication, Tumeurs Malignes Rares [6], both of which provide useful information, but have not been able to cover all relevant topics in detail needed by the clinician faced with every complex and rare condition. Increasingly, the standard oncology texts are beginning to address the more interesting or therapeutically responsive rare cancers, but also fall short.

There is no 'standard' approach to the management of uncommon cancers, although I believe that one can set a reasonable and safe structure to assist in management (Table 1). In my view, the most important first step is to secure histological review by an expert tumor pathologist. In my referral practice, it is quite common for a diagnosis of 'rare cancer' to be overturned by an expert—for example, the diagnosis of small-cell prostate cancer (absent neuroendocrine serological or immunohistochemical markers) often is actually a Gleason's 5 + 5 (undifferentiated) adenocarcinoma, which requires a very different pattern of care. Thus, I usually arrange for histological review before expressing an opinion or seeing the patient. Similarly, in the context of an uncommon presentation or an uncommon tumor type, early review of staging investigations at a center of excellence is usually worthwhile.

The next step really depends on the clinician's preference. It seems perfectly reasonable for the clinician with available time to review what is known in the literature—my own preference is to consult Textbook of Uncommon Cancer, Tumeurs Malignes Rares (if one can read French) or one of the standard textbooks (hoping to find a section on the relevant uncommon tumor type), and I also will use PUB MED, with appropriate key words, to ascertain what is known about the specific tumor. Unfortunately, much of the PUB MED information is dominated by isolated case reports, often with a gratuitous review of the literature, which is often produced by someone who is NOT an expert, and compounded by data recycling [7].

An important cautionary note is to beware of the isolated case report—these are often written by relatively junior or inexperienced clinicians, and are marred by absence of expert histological review or adequate follow-up; furthermore, an isolated case report is really only an anecdote, and hardly constitutes the basis for placing a patient at risk for iatrogenic toxicity. Furthermore, many editorial policies focus against the publication of negative case reports, thus prejudicing overall

Table 1. Schema for management of uncommon tumors

Steps in management	Rationale
Confirm histological diagnosis—by expert tumor pathologist	Extensive literature supports benefits of pathology review in centers of excellence; even more important in cases of rare malignancies
Review of radiology and other diagnostic criteria (including unusual biochemical or gene tests)	Uncommon findings can easily be misinterpreted, including radiology, biochemistry and molecular testing; quality controls may be less rigorous in this context, outside centers of excellence
Literature Review: (i) Standard texts may have relevant sections (ii) Consider Textbook of Uncommon Cancer or Tumeurs Malignes Rares (note selection biases and potential dated information in any text) (iii) PubMed or equivalent (problems summarized in text).	The textbooks are usually written by experts with extensive experience in management of specific cancers, and sometimes include uncommon patterns of presentation or rare tumors; beware isolated case reports for inaccuracies noted in the text of this editorial; beware data recycling in reviews; beware the 'case report and review of the literature'
Consult an expert—usually at center of excellence, choosing an expert with a relevant publication record or presentation record at national/international meetings	Rare tumors tend to cluster at centers of excellence, at least to the extent that expert opinions will be sought and pathology/scans reviewed
Practical consideration: set up a partnership with an expert	It may not be feasible for a patient with an uncommon cancer repeatedly to attend a center of excellence, but the expertise of such a center (including pathology and staging review) can often be shared in an active partnership with a local oncologist providing specific treatment, follow-up and data for the center.
Good questions to ask the expert before implementing his/her strategy: (i) How many of these cases have you seen and/or helped to manage? (ii) What were the outcomes? (iii) Is this experience published? (iv) How long was the follow-up? (v) Any other experts whom you consult? (vi) Do you require routine pathology review?	

assessment in favor of the positive anecdote. One of the attractions of the report from Pecuchet et al. [1] is that it has appropriately addressed these issues, and actually correlates well with the publication of recognized experts on kidney cancer [8] and other respectable series [9]; the authors indicate clearly the importance of confirming their early observations with further structured trials.

Another potential source of information is the Rare Cancer Network, founded in 1993 in Lausanne, Switzerland, by Professor Rene Mirimanoff [10], with data generated by e-mail and a dedicated website, but apparently absent central histological review. This group has summarized its work in a recently created open-access journal, and while worthy in intent, interpretation of some of their outcomes is confounded by factors listed above, and in particular centralized quality assurance.

Even where there is useful published information available, produced by experts, I think it is in the patient's best interest for the clinician without specific expertise to discuss the case with an expert in the field, or even to refer the patient for a second opinion. How does one identify such an expert? Usually it is not that difficult to identify a nationally known figure with a published track record in a specific tumor type (they usually see a broad range of uncommon variants of that tumor) or someone who has published specifically on the particular uncommon tumor. Review of the proceedings of national and international meetings will also indicate experts with specific interest in rare tumors, as do the tables of contents from some of the publications listed above. In my own referral practice, I am happy to see patients with uncommon cancers to give a second opinion, assist in the planning of management and leave much of the clinical implementation to the referring clinician(s), but with intermittent follow-up information being provided.

The problem of rare cancers remains vexing, both with regard to definition, structured approaches to treatment, and the relative lack of interest by government authorities. Recently in the United States and Europe, government health services have begun to involve themselves in the provision of resources for such patients. However, collaborative groups, such as the North American cancer trials groups and the EORTC, have not really been supported in their attempts to develop structured studies for uncommon malignancies, largely because of the focus of government funding in the domain of randomized, clinical trials. This is one area in which unfettered international collaboration could really make an impact to benefit patients and have a cumulative impact on up to 25% of incident cancer cases. Until the bigger picture is addressed at a system level, the approach summarized in Table 1 may help the isolated clinician to do a better job in this complex and challenging setting.

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disclosure

The author one of the editors of Textbook of Uncommon Cancer; he has attempted to be sensible in identifying the book (and its competitors) without suggesting that it is superior, and without using this topic as an advertorial. He is on international advisory board to President of Sanofi Aventis, but this has no relevance to this topic.

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