

Paolo Casali:

the man with the method

→ Marc Beishon

Paolo Casali specialises in sarcoma, a ‘rare’ cancer with at least 50 subgroups. Good practice, he believes, starts with a deep knowledge of the disease in front of you. This, in turn, requires a rigorous approach to clinical methodology – something he feels the cancer community should pay more attention to, for the benefit of both patient care and clinical research.

The first point any oncologist makes about rare cancers is that they are – collectively at least – not rare at all. As Paolo Casali, the medical oncologist head of the adult sarcoma medical unit at the Istituto Nazionale dei Tumori – National Cancer Institute – in Milan, states: “Even if you use very conservative definitions, at least 20% of all tumours are classed as rare – and together the whole group makes up the same number as two of the big killers. But the misconception that this group is rare means we have great difficulty getting resources to treat them.”

That misconception plays out to the disadvantage of patients in a number of ways, in particular lack of specialist centres for rare cancers and poorly coordinated research efforts. While outlying hospitals may be at a disadvantage for many tumour types, a lack of a specialised multidisciplinary team can be especially acute for diseases that are not seen on a day-to-day basis. Some rare cancer groups have made substantial progress in networking – leukaemia/lymphoma being a good example – but as Casali points out, there is as yet no fully fledged international network for adult soft tissue sarcomas, a group of dis-

eases that he says is as common as adult leukaemias.

“In fact, all rare solid tumours are, if anything, more frequent than haematological tumours, and they should be a priority now,” says Casali. “It is simply that the haematological institutions have been used to collaboration for longer and their networks are more advanced.” That’s not to say that sarcomas do not have a good deal of dedicated activity – as he adds, there are national groups in most major countries, and he comments that there is a close knit, if relatively small, worldwide community of sarcoma researchers. “Despite some long-standing controversies on certain treatments, there is a strong consensus within this community,” he says.

Meanwhile, there are encouraging developments on the wider European stage. In 2007, the European Commission (EC) started a public consultation on the challenge of all rare diseases, and submissions were received in February this year. Naturally, the oncology community made several contributions, notably from the European Society for Medical Oncology (ESMO), where Casali is the current treasurer, and RARECARE, an EC-funded project for the surveillance of rare cancers in Europe, led by



ELIGIO PAVONI

Gemma Gatta, an epidemiologist in the Milan institute, which Casali is also involved with. And in 2006, CONTICANET, a Network of Excellence funded by the EC's 6th Framework Programme, was set up to start to address the fragmentation in sarcoma work, but is, as Casali says, only at an early stage.

Other important issues that also concern Casali may be harder to address. Chief among them is the availability of approved drugs for use with rare cancers, and the role played by regulators and pharmaceutical companies. Another key topic is the conduct of clinical trials, where regulation again could come into play to increase the clinical relevance of results. "There is much interaction between regulators and the pharmaceutical industry, and between clinicians

and the drug firms, but we are missing a third side of the triangle – between ourselves and the regulators, which could help influence study design and drug availability," he comments.

Above all, given the challenges of rare cancers, Casali wants to promote far more effective networking among clinicians, and cites among his most important projects contributing to the regional network for all types of cancer in the Lombardy region of Italy, where Milan is located, and developing the Italian Network on Rare Tumours, for which he is the coordinator. The latter connects the work of Italy's major cancer centres on adult solid tumors, and Casali is keen to emulate the more advanced networks seen in countries such as Sweden.

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Focusing on optimal care is of course a priority, especially in a 'long' country such as Italy, where patients may have to travel far to find a specialist. "Sarcomas are non-epithelial tumours of connective tissue – most solid cancers are epithelial in nature – and they can arise anywhere in the body," says Casali. "So we are not organ specific. The main treatment is surgery, and good practice may be crucial for the best outcomes for sarcoma patients." Soft tissue sarcomas often appear easy to excise, he adds, and as most soft tissue masses are benign, some surgeons do not even consider the possibility of malignancy, which can result in inappropriate treatment and late referral to a specialist. "In the UK they call it the 'whoops' surgery – the surgeon cuts and then says, 'Whoops, it was a sarcoma.'"

While Casali's institute will see about half of all Italy's soft tissue sarcoma patients at some point in their history, it is common to find that suboptimal surgery has been done. "It may not affect their prognosis but they may need several additional and unnecessary operations, and suffer outcomes such as loss of limb function. But it is much harder to transfer knowledge to local hospitals about rare diseases, as you need to reinforce your learning constantly."

His institute in Milan has a dedicated sarcoma surgeon and is of course multidisciplinary overall, with integrated radiotherapy, medical oncology and pathology. "One of the main added values of our networking has been to change a lot of pathology diagnoses – the importance of pathology in groups of rare and complex tumours can't be overestimated." He mentions Paolo Dei Tos, an internationally known sarcoma pathologist who works in a small town north of Venice, as someone who plays a crucial role within the network to improve the quality of sarcoma diagnoses.

And because sarcomas are a collection of some 50 or so subgroups of tumour, Casali considers the investigational approaches to finding treatments for subtypes such as GIST are also serving as models for the more common cancers, as they too are rapidly subdividing into their own subgroups. "Even frequent tumours may become rare tumours," he says.

But there have been considerable methodological problems about some studies on sarcomas so far, reports Casali, "such that in our clinical practice we tend to do the opposite of what some of the major cooperative trials have suggested," for instance regarding the use of adjuvant and multi-therapies in advanced sarcomas.

So like many research-oriented oncologists, he is right on the cusp of all the key issues and uncertainties about progress in targeting subgroups – and sometimes subgroups of subgroups – in cancer patient populations. However, there is one point on which he is crystal clear, and which has been his mission for some time – the need for a deep understanding of the disease in front of you. "Being disease oriented and not drug oriented is my starting point as a medical oncologist."

Casali is one of those oncologists who always wanted to be a doctor, despite having no medics in his family. But like many, his path into oncology was mainly by chance. "In my last year of university I had done the usual round of surgery, internal medicine, neurology and so on, and finally I came to work at the National Cancer Institute, and I found it a very interesting environment. Back then, there was only one medical oncology department, but it was led by Gianni Bonadonna, the most famous Italian medical oncologist, and he promoted an openness that was hard to find elsewhere, and still is to some extent in Italy."

By openness, Casali means an environment where clinicians and researchers were encouraged to collaborate on an international basis. And Bonadonna, a pioneer in the adjuvant treatment of breast cancer and the development of the combination chemotherapy regimen that remains the gold-standard treatment for Hodgkin's disease, made a big impression on Casali. "Being in contact with the outside world was a big draw for me. Yes, it can be better for young clinicians to work abroad and develop connections that will last for life – I've had to work hard to do so from here – even if you won't find anything very different in the clinical approach elsewhere."

Casali worked as a clinical fellow and associate

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physician for nearly 10 years at the Institute, and then another 10 years in a full staff position as a medical oncologist, before being made head of the adult sarcoma medical treatment unit in 2004. His focus on sarcomas developed gradually over this time, and finally became his exclusive focus. In fact, his first board certificate was in haematology, before he went on to be certified in clinical oncology, and initially he was assigned to work mainly on lymphomas.

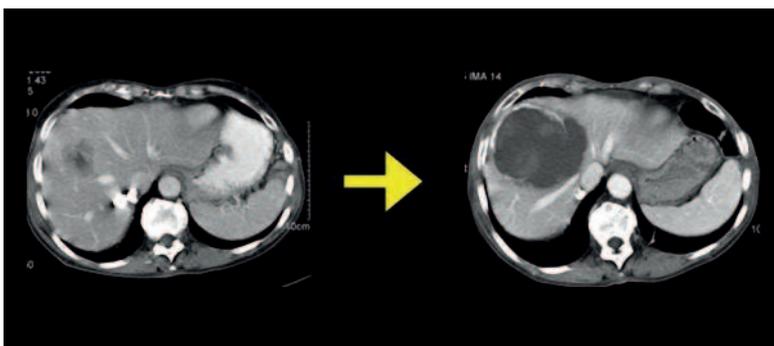
“I started looking at sarcomas in the late 1980s, when a decision was made that I would follow the disease from the clinical research standpoint. The same day I went to the library and made photocopies of all I could find on sarcomas and started studying the subject in depth – and if you do that you can start really enjoying the experience.

“I remember at the time doing my outpatient clinics on lymphomas, that the more in-depth I went on sarcomas, the more I felt I understood lymphomas. If you understand one disease in detail you are in a good position to understand others – and that’s probably because of appreciating how clinical methods work.”

Casali’s interest in the ‘clinical method’ is long standing, and indeed way back in 1991 he co-authored with Lisa Licitra and Armando Santoro a book on the topic, published in Italian. “I found that looking at the issues concerning clinical methods was very helpful to both my clinical practice and research – we looked at concepts such as tumour response, quality of life, staging, follow-up and so on – all the areas that have to do with clinical methods in oncology. As two young oncologists at our world-renowned institute, it struck Lisa and me that no one had paid much attention to many of these issues, and it is still a problem.”

He takes tumour response as an example. “I feel that the medical oncology community has not approached this from a conceptual point of view, relying instead on convention. Tumour response was defined by David Karofsky as a 50% decrease in the main area of a lesion, but there is no reason why 49% or 51% is not a response. The convention is not based on clinical or biological grounds – it’s just a way of talking about the same thing, and nothing much has been done to refine the convention.”

With the new targeted drugs, the problem has become clear. As a graphic illustration, he shows before and after slides of liver lesions from a GIST



patient who has received Glivec (imatinib), where in the second the lesions are bigger. “But if you do a biopsy you don’t find as much tumour and the patient is actually responding. Using the Karofsky definition, it would be seen as a progression not a response.”

It is one element of understanding how this sarcoma subgroup works, and of course one of the great success stories in targeted therapies is Glivec and GIST. Because of its similarity at the molecular level to chronic myeloid leukaemia, GIST was the logical second tumour to research for the drug, and trials have shown major survival in those with advanced cancer.

Casali stresses how important it is to take a disease-oriented, clinical approach to treatment and research, especially with groups such as sarcomas. “While we have big improvements in GIST, in other sarcomas it has been difficult to show gains with drugs because the main treatment is surgery. But if you look at the Eurocare data, big differences were shown in the past between west and east Europe, which must depend on something – mainly the multidisciplinary approach, although that’s hard to prove as you have selection biases when comparing centres. But I feel quality of care and multidisciplinary must mean something – and here in Milan, for example, our sarcoma surgeon Alessandro Gronchi is directly involved in helping to highlight the activity of drugs, and we are involved in his work.”

This disease focus has led to clinical practice that is at odds with the results of some sarcoma chemotherapy trials, particularly the large trials such as those run “very rigorously” by the European Organisation for the Research and Treatment of Cancer (EORTC). “Many sarcoma oncologists tend to favour adjuvant chemotherapy and multiagent chemotherapy in advanced disease, which are the

A question of method. Using the standard RECIST measure of response, this liver lesion appears to have progressed on a CT scan, but a biopsy would reveal the opposite to be the case

opposite conclusions of the trials,” he says. Meanwhile, particular contributions his team has made include clinical observations of response to trabectedin (Yondelis), a new marine-derived drug, in myxoid liposarcoma, and of Glivec in chordoma, a very rare type of sarcoma. “When we treated the first patient with advanced chordoma, it was only when we looked at the slides in the same way as we’d learnt to do with GIST that we understood he was responding,” he adds.

The reasons he and also others choose not to rely on the major randomised cooperative trials mainly concern the limitations of applying findings of large-scale trials directly to the bedside. Two issues, in particular, are lack of specificity in the study populations – mixing high- and low-grade tumours for example – and lack of clinical input to the study designs, such that biases about aspects such as surgery may be present. “It is often the case that clinicians are not involved in the methodology of clinical studies as much as they should be – we often don’t understand the language of medical statistics and so do what the statisticians say.”

This is not to say that the major trials are not valuable – Casali is a leading participant and coordinator in existing work and a strong advocate of much larger and inevitably more expensive intergroup studies. But, as he, with Licitra and Paolo Bruzzi, noted in an editorial on reporting clinical trials and meta-analyses (*Annals of Oncology*, August 2000), clinical decisions are very complex and are influenced by many factors, and oncologists need to take into account other sources such as phase II studies, case series, and much other descriptive knowledge. Randomised trials also provide more information than the simple ‘P-value’, while of course randomised studies with sufficient power will never be carried out on a lot of clinical issues, especially on rare tumours. A new clinical method that tailors evidence to patients, often with elements of subjectivity, is needed – a proposition that formed the basis of the editorial.

In turn that means open discussion with patients about the uncertainties with treatment, quality of life

and cost. Casali is involved with drawing up ESMO’s sarcoma guidelines but is also one of the organisers of START – State of the art oncology in Europe – a website that has tumour-specific information designed, he says, to help doctors and patients explore a more individualised approach. START is administered from Milan but has a Europe-wide input (see startoncology.net). As an example of how finely balanced one of sarcoma’s enduring controversies is, he mentions a ‘for and against’ debate on adjuvant chemotherapy at an ESMO conference in Istanbul. “I spoke for, and Ian Judson of the Royal Marsden against, but we agreed that we were using essentially the same slides with the same premises. Overall there is a broad consensus in the sarcoma community, although the clinical decision for the individual patient may be different. But this is not a problem, as long as the patient is involved in the uncertainty of decision-making.”

At national and European levels, Casali would also like to see regulators setting out in more detail how clinical trials should be conducted. “The design of trials should be as targeted as the drugs are – and as the regulators share study designs with the pharmaceutical companies they can influence them from the start by listening more closely to the research communities.” Without more direction, he feels the methodological problems of investigating subgroups in rare tumours will continue to be a major issue, and costs of new drugs will be unbearable if their use is not ‘targeted’.

Then there is the issue of availability of both new and old drugs for rare cancers, and here Casali makes two key points. “First, we now have rules on orphan drugs that give incentives to pharmaceutical companies to develop drugs for rare tumours. That’s an achievement the European Medicines Agency and the EU must be proud of. But the incentives only apply to approved drugs, and companies may decide not to register drugs if they feel the risk of trying to provide the same quality of evidence as that required for trials on more frequent tumours is too high.

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use, which is very common in oncology. It does not just involve new drugs – there are a lot of older drugs which companies will never ask to have registered for certain tumours now. But the industry is the only party entitled to register a drug.” His concern is that oncologists take on a higher, and possibly legal, responsibility when they use off-label drugs, and that varying patterns of reimbursement and policies for allowing their use will give rise to inequalities around Europe. “Each country is trying to address this problem differently.”

There are, for example, certain off-label cytotoxic chemotherapies that are showing activity in sarcoma subgroups, and Casali feels the best way forward is to establish standard medical compendia that, in practice, give a green light to the use of some off-label drugs. This is in place in some European countries, and also in the US, where it was set up by the state Medicare programme, but is also broadly followed by private insurance agencies. That this is a big issue is evidenced by an editorial Casali wrote last year on behalf of ESMO in the *Annals of Oncology* (2007 18:1923–25), and he says the society will be surveying oncologists to gain a more detailed picture of how policies differ around Europe.

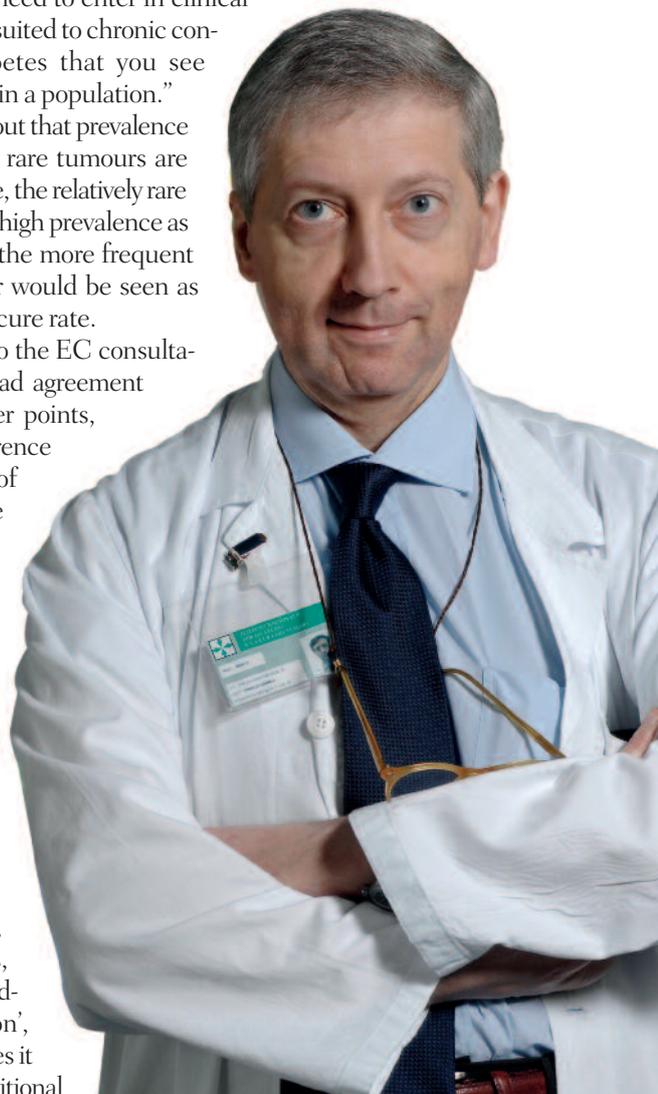
In fact ESMO is very much taking this and other issues to decision makers at the European level. Having succeeded this year in getting a European Parliament resolution passed on EU-wide recognition of medical oncology as a specialty, their main priority is to get this implemented. Other efforts include highlighting issues with rare and difficult-to-treat cancers, which will be the subject of an event hosted by ESMO in Brussels in early November. Casali and colleagues intend to put drug availability and related issues to the fore, including a discussion on improving the methodology of the development of new drugs for rare tumours.

Clearly, the recognition by the EU that rare diseases need particular attention is welcome, but as Casali notes, the very first part of the consultation exercise – defining what a rare disease is – immediately becomes a problem for oncologists. “The defi-

inition is based on prevalence of disease, not incidence,” he says. “While we must respect prevalence as a definition – the rules on orphan drugs are based on this – incidence is much more appropriate for cancer, as events only happen once in this disease. Incidence allows us to estimate the number of people, say, having surgery and first-line chemotherapy, and also the numbers we need to enter in clinical studies. Prevalence is suited to chronic conditions such as diabetes that you see through people’s lives in a population.”

Further, he points out that prevalence can greatly skew how rare tumours are identified – for example, the relatively rare testicular cancer has a high prevalence as it is very curable, but the more frequent small-cell lung cancer would be seen as rare, thanks to its low cure rate.

In its submission to the EC consultation, ESMO is in broad agreement with most of the other points, such as setting up reference networks – which of course cannot come fast enough for Casali. CONTICANET, which is headed by his good friend Jean-Yves Blay, professor of medicine at the Université Claude Bernard in Lyon, “could be the embryo of a soft tissue network at last.” It aims to overcome difficulties with ‘lack of data, mobility of researchers, heterogeneity of methodologies and legislation’, and Casali has big hopes it will help overcome traditional



obstacles to pan-European working. He sees regional collaborative networks, where patients are managed over a wide area, as crucial to avoid 'health migration' to centres such as Milan, with consequent long waiting lists.

Even in one of Italy's premier cancer centres, however, there are major resourcing problems. Casali's sarcoma unit, for example, has ten physicians, but only two – himself and long-time colleague Rossella Bertulli – are permanent staff. The rest – among them international names in the sarcoma community – are funded mainly by research money. It is not surprising that when he is not on international work Casali spends most of his time in the clinic and in tumour board and pathology meetings, and other activities in his unit. His one other internal role is secretary of the Institute's ethics committee for clinical trials, which he says gives him insights into issues such as how samples from hospitals that may contribute only a few patients can be controlled by the sponsors, leaving academic researchers such as biologists out of the picture. "We are debating in Italy now how tumour samples are used in clinical studies," he says.

An advantage of working with rare cancers is, however, that pharmaceutical companies are more open to direct collaboration with clinicians. "It's a privilege for us because the sarcoma community is so small and, of course, we can also try methodological solutions that are not followed in more frequent diseases, which again is why I further believe we can be a model for oncology as a whole."

Casali does a little teaching at postgraduate level and says young oncologists are wary at first about working with rare tumours. "Then they find that you can learn clinical methods no matter what disease you work on and that it is great to go into depth." No doubt he is keen to be a good role model for his thinking on the clinical method – when asked to cite mentors, he can more readily suggest people who showed him what not to do. "I've found a lack of interest in clinical methods, but what worries me most are people who are too conservative and don't want to try new things." Running up against such department heads

has been his main professional barrier, he says. "Although by instinct I am a bit conservative myself, I always wonder how to change things."

People who will be doing less wondering and taking more action, says Casali, are patients. "We can now add advocacy groups as a third category of trial sponsor to the industry and academic sectors. I believe they will drive a lot of research in future. More and more patients will not join studies that the groups do not approve of and this will be critical for pharmaceutical companies, which are also supporting these groups. It's a complex scenario, with potential conflicts of interest. But doing anything always implies conflicts of interest – disclosure is a good remedy."

A patient-driven study he mentions investigated Glivec doses in GIST, and he was also taken aback when at a GIST meeting patients presented a study disregarding the 'intent to treat' principle in analysing data. "I said I'd never heard in any medical congress someone challenging the principles of clinical research. However questionable all that could be, I thanked them for their radical thinking, as they don't have the luxury of waiting for survival data at the end of trials. I am thinking now of involving patients in the ESMO recommendations on GIST." A particularly active advocacy group is the US-based Life Raft, which is laying down its own model for allocating GIST research funds, in a similar way to other groups such as the Multiple Myeloma Research Foundation.

Casali has little in the way of distractions outside of work. Indeed, he says that pursuing some of the issues surrounding sarcoma, such as lobbying European decision makers and writing on the clinical method, are his 'hobbies', alongside chess, which he views in much the same light as clinical decision making. "Instead of collecting stamps I look at clinical ethics," he jokes.

He has no immediate plans beyond staying at the Milan unit and his priorities of extending the networks in Italy and Europe, and is not likely to change course from sarcoma and rare disease. But one hopes he will find time to write about the clinical method – in English this time of course.

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