AIOM

Necessary steps to cope with rare cancers in Italy

Passi necessari per affrontare i tumori rari in Italia

Associazione italiana di oncologia medica (AIOM)

Rare cancers are neoplasms with an annual incidence of less than 6 cases per 100,000 inhabitants; altogether, they account for as many as 25% of all cancer cases.[1,2]

Rare tumours pose particular problems for health system organisation, assistance, research, and new drug approval and reimbursement.[2,3]

Following current methodologies, clinical trials need a high number of patients to reach statistical significance, and it is not easy to collect such a number for uncommon tumours.

As a consequence, clinical evidence is more complicated to reach in rare than in frequent cancers. The final result is a high level of uncertainty in the whole process of decision making.[2-4]

Lack of evidence, low levels of recommendations, poor expertise of pathologists and clinicians lead, in general, to worse treatment results and worse survival in patients with rare cancers, compared to those recorded for common tumours.[1-4]

However, there is a great variance in incidence, natural history, and treatment outcomes among the groups of rare cancers.[5]

For instance, the highest 5-year survival level is recorded in testicular tumours, whereas, at the other extreme, mesothelioma has the lowest; both are considered rare cancers.[5-7]

Late diagnosis, incomplete or wrong pathological reports, and suboptimal treatment are frequent in uncommon tumours.[2-4]

For about 15 years, efforts have been made to improve knowledge and outcomes in rare cancers.[1-4]

As with more frequent types of cancer, decision making should be addressed rationally. Clinical studies must provide physicians, patients, and families with informative results which can be useful in the choice of the right therapy.[2,3,5,6]

A structure comprised of referral centres (hubs) with a higher expertise in a specific rare cancer, leading minor centres (spokes) grouped in a reference network, is at present the most accepted solution in health organisation.[1-5]

Earlier and more precise identification and diagnosis of an uncommon tumour and consequent decision making are essential to cure a higher percentage of patients, increase the number of long-term survivors, and lower the costs of management.[2-4]

A review of the pathologic diagnosis performed in hub centres is the first, fundamental step in the treatment of a rare tumour.[2-4,9]

Concordance between initial diagnosis and referral centre review is required.[9]

The exchange of experience, with ongoing communication between the hub and spokes, is crucial.[2,3,11]

However, the «rare tumour» label groups many entities, different for histology, anatomic presentation, natural history, and prognosis.[5]

The best example comes from soft tissue sarcomas (STS), one of the most studied groups of rare tumours. They can arise from fat, muscles, tendons, vessels, peripheral nervous system, and visceral organs. Almost all anatomic sites can be involved and more than 50 different histological types are recognised.[8]

Such a complexity requires a high level of expertise from a variety of specialists: pathologists for a correct diagnosis, surgeons performing interventions, orthopaedists for STS of the extremities and girdles, gynaecologists for uterine sarcomas, abdominal surgeons for retroperitoneal sarcomas, thoracic surgeons for lung and chest sarcomas, and otolaryngologists for head and neck sarcomas.[2,3,9]

Radiotherapy and medical treatment also require a particular expertise.

Since rare cancers include more than 200 entities, it is easy to understand that nobody can be a global expert in all these tumours.[1,2]

Searching for a referral centre, very often the patient has to move from the area of residence to a distant specialised hospital, in order to get the highest level of care. This solution increases personal and family costs.

In the hub/spoke system, on the other hand, the patient has to move to the referral centre only for brief phases of treatment, requiring high expertise. Ordinary therapies can be offered at the closest spoke hospital connected with the hub.[2-4]

How many referral centres should be planned in Italy to cope with all rare cancers?

Grouping the uncommon cancer by anatomic site, it is conceivable that a centre every 15-20 million inhabitants could be planned.[2-4]

In any case, the rarity of these tumours and the uncertainty in diagnosis and treatment do not modify the process of decision making applied in more frequent tumours.[2]

A multidisciplinary approach is the preferred model of health organisation in uncommon tumours,[2-4,9] with certain limitations: if the multidisciplinary group is unbalanced with expertise levels varying between the components, results can be less than optimal.[2-4]

Adequate training of all members of the group, steady communication with referral centres, and a periodical review of final results are necessary. Implementation and sharing of approved guidelines and constant monitoring of outcomes are fundamental to increase the group's experience and skills.[2-4]

Precise pathological diagnosis, well-defined staging of disease, and accurate clinical evaluation of the patient can lead to precise planning

of treatment. The complete evaluation of a treatment's risks and benefits must be shared with patients and their family and patient preference must be taken into account in the final decisions.[2-4,10]

Rare tumours have a specific profile in clinical studies, too. Because of the low number of patients, low levels of evidence are normally reached. When large and randomised trials are not feasible, evidence can be derived from single case reports, uncontrolled trials, and observational studies.[2,11]

Observational studies on selected patient subgroups can make it possible to collect important pieces of information on natural history and clinical characteristics in tumours which sometimes have only a pathological description.[2,8,11] National and international collaborations should be pursued.[2,11]

Another solution is to use non-frequentist or Bayesian statistical approaches.[11,12] Each piece of data must be recorded to increase knowledge: to this purpose, a wide and well-equipped data network is crucial in rare cancer cooperation.[11]

Quality control programs between hub and spokes should be planned in order to ensure data quality. Research networks must improve the knowledge and level of care of rare cancers.[2,5,9,11]

Collaborative studies involving hub and spokes can prove important to improve the quality of diagnosis and treatment.[11]

In rare cancers, planning clinical studies on new agents is strongly encouraged and pharmacological companies receive support to develop orphan drugs.[11]

Patients should be informed about ongoing trials and close cooperation with patient advocacies is mandatory.[2,3,11]

Sometimes, off-label application of a new treatment, if ethically correct, could be considered as a solution in order to shorten the time of approval of an innovative therapy.[11]

On the other hand, regulatory agencies, national health systems, and insurance companies have to guarantee equality among patients with common and rare tumours.

In rare cancers, less strict rules on compassionate use, approval, and reimbursement of new drugs is recommended, taking into consideration the higher level of uncertainty in rare cancers.[2]

The role of scientific societies such as the Italian Association of Medical Oncology (AIOM) is to support modern, high-quality cancer treatment, encouraging in rare cancers a multidisciplinary and multispecialty approach. The care of patients must be carefully planned and coordinated from the outset with all specialists meeting together.

Another important role of AIOM is to act as a stakeholder to evaluate the treatment of rare cancers in order to cooperate with the Italian Agency for Drugs (AIFA) and reduce procedures and timing in introducing new active drugs.

The assessment of orphan drugs must be encouraged to facilitate pricing and payback for a new treatment.

Furthermore, AIOM must support the role and function of the scientific societies created to study rare tumours, actively cooperating with national and international organisations such as the Italian Network for Rare Tumours (RTR) or European Society for Medical Oncology (ESMO) – Rare Cancer in Europe.

But the highest commitment of AIOM is to improve the educational level of oncologists by promoting, editing, and implementing national guidelines on rare tumours.

AIOM has recently produced six National Guidelines on Rare Cancers on:

- neuroendocrine tumours;
- CNS tumours;
- soft tissue sarcomas, GIST and gynaecologic sarcomas;
- oesophageal cancer;
- bile duct and gallbladder cancer;
- testicular tumours.

The next step will be the completion of guidelines on more rare tumours, such as mesothelioma, thymoma, salivary gland tumours, small intestine and appendicular tumours, vulvar and penile carcinomas.

Close cooperation with other Italian scientific societies, such as the Associations of radiotherapists and pathologists, and various surgical societies, is necessary.

The final goal is to transform the present AIOM guidelines into national, multidisciplinary, shared guidelines, approved by the Ministry of Health, to be used academically in Italian schools of medicine and specialisation.

Finally, the guidelines should be translated into English, to facilitate diffusion in other countries.

REFERENCES

1. Gatta G, van der Zwan JM, Casali PG et al. Rare cancers are not so rare: the rare cancer burden in Europe. *Eur J Cancer* 2011;47(17):2493-2511.
2. www.esmo.org/Policy/Rare-Cancers-Europe
3. ESMO/European Sarcoma Network Working Group. Soft tissue and visceral sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2014;25 Suppl 3:iii102-112.
4. AIOM. *Linee Guida. Sarcomi dei tessuti molli e GIST. Edizione 2015*. Available from: http://www.aiom.it/C_Common/Download.asp?file=/$Site$/files/doc/lg/2015_lg_aiom_sarcomi.pdf
5. Raghavan D, Brecher ML, Johnson DH, Meropol NJ, Thigpen JT. *Textbook of Uncommon Cancer*. 4th edition. New York, Wiley, 2012.
6. Gatta G, Ciccolallo L, Kunkler I et al. Survival from rare cancer in adults: a population-based study. *Lancet Oncol* 2006;7(2):132-140.
7. De Angelis R, Minicozzi P, Sant M et al. Survival variations by country and age for lymphoid and myeloid malignancies in Europe 2000-2007: Results of EUROCARE-5 population-based study. *Eur J Cancer* 2015. pii: S0959-8049(15)00778-9. doi: 10.1016/j.ejca.2015.08.003. [Epub ahead of print]
8. Fletcher CDM, Bridge JA, Hogendoorn PCW, Mertens F (eds). *WHO Classification of Tumours of Soft Tissue and Bone. Fourth Edition*. WHO Classification of Tumours Volume 5. Lyon, IARC, 2013. Available from: http://apps.who.int/bookorders/anglais/detart1.jsp?codlan=1&codcol=70&codcch=4005
9. Ray-Coquard I, Montesco MC, Coindre JM et al. Sarcoma: concordance between initial diagnosis and centralized expert review in a population-based study within three European regions. *Ann Oncol* 2012;23(9):2442-2449.
10. Thornthon JG, Lifford RJ, Johnson N. Decision analysis in medicine. *BMJ* 1992;304(6834):1099-1103.
11. Casali PG, Bruzzi P, Bogaerts J, Blay JY, Rare Cancer in Europe (RCE) Consensus Panel. Rare Cancers Europe (RCE) methodological recommendations for clinical studies in rare cancers: a European consensus position paper. *Ann Oncol* 2015;26(2):300-306.
12. Adamina M, Tomlinson G, Guller U. Bayesian statistics in oncology: a guide for the clinical investigator. *Cancer* 2009;115(23):5371-5381.