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doi:10.1093/annonc/mdz165
Published online 22 May 2019

Rare cancers: from centralized referral to networking

In this issue, Blay et al. report that in a French database including nearly 30 000 sarcoma patients, treated between 2010 and 2018, surgery was carried out at centers belonging to the French sarcoma network in a proportion of cases that rose from 30% to 40% across years. Outcomes were superior to surgery carried out outside the network, in local relapse-free survival (LRFS), event free survival and overall survival (OS) [1]. The French effort, including its commitment to outcome reporting, should be warmly congratulated. While it is desirable that similar efforts are replicated in other cancers and other health systems, one may wonder where we are with models of networking in rare cancers.

The first reason for congratulating the French effort is obviously that a sarcoma network was actually established in a big European country of >65 000 000 citizens. Then, the network was funded under the umbrella of the French government. This made it possible that, by 2017, >50% of French sarcoma patients were discussed by a multidisciplinary tumor board (MDTB) before their first treatment. Importantly, this was paralleled by a systematic pathologic review of all cases, in a disease that is marked by more than one-third of inappropriate pathologic diagnoses outside reference centers [2]. Finally, by 2013, the clinical database has included almost all new incident sarcoma cases in France.

So, what's next? An obvious way forward would be simply quantitative. If more than 40% of patients were not discussed upfront by a sarcoma MDTB, including more than one-third of those treated within the network, numbers can increase. However, even such a simple indicator provides a good example of how qualitative progress could be fostered by refining the methodology of multidisciplinarity and networking. Regarding multidisciplinarity, in fact, we could easily discover how varied amongst centers are the formats of MDTP case discussions. Some institutions discuss all new cases, while others only the problematic ones; some discuss only local-disease cases, others metastatic; some discuss patients only at the beginning of their clinical history, others those requiring any change in treatment strategy. At a high-volume center, discussing all cases may mean that the discussion could be useless for most and too short for the most complex. However, limiting the discussion to the latter requires that the MDTP has reached a good consensus about treatment criteria and a high knowledge of the disease is spread across all its members. This will be the case only at centers with truly high case volumes.

A crucial issue about the methodology of networking is implied thereby. The French sarcoma network includes 26 centers. With roughly 4000 new sarcoma cases in France yearly, each would treat 150 new patients on average. However, two centers saw ∼10% of the total number of patients, and six more than 5%. Eleven saw <2.5%, which, in terms of new cases, would mean <100 patients yearly. Indeed, three "coordinating centers" are foreseen and a centralized review of pathologic diagnoses is in place. This corresponds to a "hub and spoke" logic. It is important to realize that building a network does not merely mean to select a number of centers of expertise. Conceptually, this would be exactly opposite to a true network. It would be a centralized patient referral, which is obviously able to improve quality of care substantially, but has drawbacks, in terms of health migration and discrepancies in access from implicit rationing of limited resources. On the contrary, networks may allow a relatively wide number of centers (spokes) to collaborate with a limited number of reference centers (hubs), by virtually centralizing some services (e.g. pathologic diagnosis), referring some patients for selected procedures (e.g. surgery), directly carrying out other treatments (e.g. medical therapy), within a clinical strategy continuously shared with an MDTB on a case-by-case basis. Spokes will continuously gain experience, in a virtuous circle of quality improvement. This is networking. However, networking is not easy to set up, manage, or fund. And the model is far from being optimized in the real world. For example, while quality

criteria for hubs have been devised in the sarcoma area [3], which quality criteria spokes should comply with? Not those based on case volumes, by definition. The ongoing EU European *Joint Action on Rare Cancers* (JARC) is working on criteria pertaining to the network patient's journey, rather than to the network spokes in themselves. Again, how can the extra medical workload be compensated to institutions, in order not to discourage them from engaging in networking? And how can a multidisciplinary patient–physician shared decision-making be implemented in a network?

The paper by Blay et al. reports an absolute difference of around 10% in OS and somewhat higher in LRFS. Of course, a favorable selection bias could be in place (but the reverse may also be true, since, say, the most challenging surgical cases are often sent to centers of expertise from the community). As a matter of fact, a $\geq$10% absolute gain in patient outcomes would be what many innovative and expensive new health technologies, e.g. new anticancer agents, may be able to provide currently. Sarcomas are a good example of rare adult solid cancers [4]. Thus, for the oncology community, investing in improving healthcare networking in rare cancers could be as rewarding as investing in cutting-edge clinical research. In the European Union, three *European Reference Networks* (ERNs) on rare cancers are now striving to improve quality of care [5]. The ongoing JARC as well as the multistakeholder *Rare Cancers Europe* effort, launched by the *European Society for Medical Oncology* (ESMO) in 2008 and now opening up to *Rare Cancers Asia*, are betting on networking to enhance quality of care in rare cancers. It is up to us all to improve the models of networking in the real world.

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Funding

None declared.

Disclosure

In the last years, the author has had honoraria for speaker, consultancy or advisory role from Bayer, Deciphera, Eisai, Eli Lilly, Nektar Therapeutics, Pfizer. At author's institution, author's unit received funds from Advenchen Laboratories, Amgen Dompé, AROG Pharmaceuticals, Bayer, Blueprint Medicines, Daiichi Sankyo, Deciphera, Eisai, Eli Lilly, Epizyme Inc., Glaxo, Karyopharm Pharmaceuticals, Novartis, Pfizer, PharmaMar.

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doi:10.1093/annonc/mdz146
Published online 2 May 2019

Anti-PD1 treatment of advanced melanoma: development of criteria for a safe stop

Treatment with programmed cell death protein 1 (PD-1) inhibitors has transformed the outcome for patients with melanoma. Recent publication of the 5-year follow-up of the Keynote 006 study reported a median overall survival (OS) of 38.7 months (95% confidence interval 27.3–50.7 months) and 5-year OS rate of 43.2% for pembrolizumab-naive patients [1]. For CheckMate 067, the updated 4-year survival was 53% for the ipilimumab + nivolumab combination and 46% for nivolumab alone [2]. Based on these results, treatment with the first-line PD-1 +/- CTLA-4 inhibitor is a standard of care for the majority of melanoma patients with unresectable or metastatic disease. These pivotal studies evaluated different treatment durations, with a maximum of 2 years of pembrolizumab in Keynote 006 and no defined maximum treatment duration time in CheckMate 067. For the latter, 11% of patients alive in the combination arm and 25% of patients in the nivolumab arm were still on treatment at the 4-year follow-up time point. An important question is whether it is safe to stop treatment at 2 years or earlier. What have we learnt so far?

First, data from these and other studies in the metastatic and adjuvant settings show that outcomes with immunotherapy are not compromised in patients stopping treatment early because of treatment-related toxicity [3–5]. Second, pooled analysis of the CheckMate 066, 067 and 069 studies showed that patients achieving a complete response (CR) to treatment had a significantly better OS when compared with those with a partial response (PR) or stable disease (SD), both for single-agent nivolumab and ipilimumab + nivolumab combination: the 3-year OS was 94% for patients achieving a CR and 45% for those achieving a PR [6]. What about elective discontinuation of treatment?

The Keynote 001 study looked at different doses and durations of pembrolizumab in 655 melanoma patients [7, 8]. One hundred and five (16%) patients had a CR and 67 of these stopped treatment electively. With a median time on treatment of 23 months (8–44), the median time of treatment after CR was 7 months, and a median time off treatment of 30 months. Sixty one (91%) responses were maintained, four patients progressed and two patients died due to unrelated causes. The Keynote 006 study trial evaluated two different pembrolizumab regimens compared with ipilimumab [1]. Of the 556 patients treated with pembrolizumab, 103 (18.5%) completed 2 years of treatment and discontinued pembrolizumab.