The influential and inspirational Gianni Bonadonna’s life commitment to evidence-based cancer medicine

Last 7 September 2015 Gianni Bonadonna passed away at age 81. He was a leader who influenced generations of clinical oncologists and left a never ending trail of outstanding achievements that have formidably contributed to shape the field of clinical oncology as we know it today. When he proposed it, applied it and proved its worth, the use of systemic adjuvant therapy of breast cancer was a radical departure from the tenets of his time. Countless surgically treated cancer patients who were destined to relapse and die have so been saved. That was his trademark and that is his legacy: there is always something better to do for the benefit and wellbeing of cancer patients, no matter how far from conventional wisdom will take you to grab that improvement. He has been a relentless innovative thinker, a fearless pioneer, but also a careful planner obsessed with the quality of the data and the reproducibility of results. He was an inspiration and a challenge for generations of oncologists. His success did not lead to arrogance, and left little room to celebration: next challenge was always the best one. He was a true gentleman inspiring great loyalty from those privileged to work with him, and felt the duty to foster by his writing and his masterful presentations the widest possible awareness and application of the advances he had led. When reviewing his many accomplishments, it appears clear that his impact extended well beyond the >500 publications and his many internationally recognized areas of expertise, including drug development, treatments of Hodgkin’s disease, adjuvant and neoadjuvant therapy of breast cancer to name the most prominent. His most formidable legacy has been that of adopting and applying to clinical oncology the firm criteria that a clinical experiment must be designed and conducted as rigorously as any laboratory experiment and to teach that intellectual rigor around the world. To adequately review Dr Bonadonna’s research and its impact would take volumes, so here we provide just a brief summary of some highlights and achievements. Dr Bonadonna’s pioneering work in the area of combination chemotherapy. In his vision combination chemotherapy was the optimal way to deliver cancer treatment. Since medical oncologists need to know how, how much, and how often anticancer drugs should be administered to their patients, the relevance of pharmakokinetic and pharmadynamic studies to clinical practice was very clear for him [1]. He pioneered the success of doxorubicin and the first step toward a formal set of rules for new drug development in oncology. The first clinical report on adriamycin (doxorubicin), the 14-hydroxydaunomycin derivative, dates back to almost a half of a century ago [2]. The initial findings [3], indicating a broad spectrum of antitumor activity as well as cardiac effects, were confirmed within a few years in large case series all over the world [4]. He is the father of the ABVD to cure Hodgkin’s disease, still considered the gold standard for Hodgkin’s disease and associated with a significantly lower potential for leukemogenesis and gonadal toxicity [5]. This four-drug regimen included adriamycin, bleomycin, vinblastine, and dacarbazine. A pilot study activated in 1973 showed that ABVD chemotherapy was at least as effective as MOPP in inducing durable remissions in advanced Hodgkin’s disease [5]. Later, a larger randomized study, which also included radiation therapy, proved that ABVD was able to improve long-term treatment outcome compared with MOPP [6]. He activated a prospective trial in patients with early, clinically staged Hodgkin’s disease to assess efficacy and tolerability of four cycles of ABVD followed by either subtotal nodal plus spleen irradiation (STNI) or involved-field radiotherapy (IFRT), pioneering the modern combined approach of chemotherapy and radiotherapy in Hodgkin disease [7]. Dr Bonadonna was the first medical oncologist to propose pediatric oncology as a stand-alone discipline in Europe [2]. He anticipated the ethical burden of pediatric oncology trials, which are conducted in a highly vulnerable population of severely ill children with cancer addressing also the issue of survivorship. In 1975, he presented the first report on the efficacy of cyclophosphamide, methotrexate, and fluorouracil (CMF) delivered in 1-month cycles for 12 months as adjuvant treatment for node-positive breast cancer [8, 9]. These results, along with those reported in a similar patient population by the National Surgical Adjuvant Breast and Bowel Project [10], raised hopes that chemotherapy could have a more central role in the primary management of this common cancer, and were of seminal importance for all the studies on adjuvant systemic therapy conducted throughout the world. The long-term analysis of the CMF trial, after a median follow-up of 25 years confirmed that a longer duration of the same drug regimen was unable to improve treatment outcome [11]. In response to the early results observed in the above-mentioned study, in the early 1980s, Dr Bonadonna’s group tested in a random fashion whether the inclusion of a non-cross-resistant agent such as doxorubicin (DOX) could be of benefit in patients with breast cancer and positive nodes [12, 13]. In women at high risk of disease relapse because of extended axillary involvement (>three positive nodes), he reasoned that DOX, either given first and followed sequentially by CMF or interspersed with CMF, had the potential to improve treatment outcome [12]. A 20-year analysis confirmed the superiority of the sequential delivery of DOX as first treatment for four cycles followed by i.v. CMF (DOXCMF) compared with the alternating delivery of the same regimens (CMF/DOX) [13]. He had the vision of the adjuvant approach in solid tumors anticipating...
the idea of micrometastatic disease. His priorities were ‘a better identification of patient subsets who are true candidates for chemotherapy, endocrine therapy, both modalities, or no systemic therapy at all. Thus, an operational hierarchy of old and new prognostic variables will remain to be clearly assessed through prospective case series and multivariate analyses. In the near future, appropriate studies should be designed to better define optimal treatment sequences, drug doses and combinations (with and without growth factors), intervals between courses, and optimal duration of treatments. In other words, we should begin to study how to properly tailor treatments for each prognostic subset’ [14]. Dr Bonadonna’s group introduced the concept of ‘primary systemic treatment’. Neoadjuvant chemotherapy was introduced in 1973 in his multidisciplinary approach for locally advanced (T3b–T4 or stage III) breast cancer [14, 15]. He anticipated the idea that pathological complete response was a surrogate of outcome: ‘it is also clearly emerging that not only is the response rate inversely related to the initial tumor volume, but the degree of tumor regression (i.e. complete pathologic remission, moderate remission, or minimal response) appears to represent a marker of outcome’ [16]. In his opinion, the real question to answer through prospective, randomized trials was not whether the shift from adjuvant to neoadjuvant chemotherapy could result in a superior outcome, but rather how to properly integrate effective primary and adjuvant drug regimens to maximize tumor cell kill. He postulated a more-refined risk assessment approach (e.g. using tumor grade or proliferative index). His proposed approach was to also allow for a wider use of tumor biopsy to obtain the primary diagnosis of cancer and of biological features, a more uniform adoption of breast-conserving surgery, and use of response to chemotherapy as a marker of treatment outcome [16]. One of the most important achievement of Dr Bonadonna was the commitment in serving patients’ interests in large clinical trials. In his view for many patient groups, transparency in study design, data collection and analysis, and full publication of results are issues of paramount importance. Together with Umberto Veronesi, he created a clinical trial office at Istituto Nazionale Tumori in Milan, and he later instituted the Michelangelo Foundation. He introduced the methodology of controlled clinical trials in medical oncology. Concerns have been raised in recent years about the misreporting of trial results and we note a push by pharmaceutical companies for greater control of clinical trials and data, outside the framework of academia. In his view, a more equal partnership between academic researchers and the pharmaceutical industry is better for patients, especially those in early stages of disease for whom over-treatment and adverse side-effects are important considerations. He pioneered an idea of academy research within cooperative groups exploring trial results in detail to derive hypotheses that may eventually lead to even more precisely tailored treatments for future patients, maintaining data control to serve the interests of the patients. Such efforts often require translational research investment and prolonged follow-up, beyond that needed for commercial drug registration. His idea of academic research should be an example in an era where pharmaceutical companies are increasingly attempting to recruit academic investigators to conduct trials in which the data are controlled by the company outside the framework of a research cooperative group or a network of academic centers. The achievements of Dr Bonadonna should inspire new generations of clinical oncologists to overcome the obstacles to a more successful control of cancer only with solid scientific objectivity and purpose, without depleting their energies and time in working frantically on projects purported to be of immediate therapeutic significance.

A last consideration is most due to Gianni Bonadonna. All his achievements went to a sudden stop one afternoon in 1995, when a catastrophic personal illness ended his active role in the arena of clinical oncology. After recovering from the acute effects of the illness, he decided to devote his energy to tell and write his last and key lesson to doctors, that of the crucial relevance of empathy and human attention to the patients. Hail to a great man and to a life well lived.

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references

Annals of oncology in 2015: the year in review

In 2015, the oncology arena has continued to evolve at an accelerated pace, with exciting novel developments notably in the fields of immunotherapy, precision medicine, epidemiology and the health economics of cancer care. This evolution also holds true for *Annals of Oncology*, which recognizes the need to adapt to meet the needs of this changing face of oncology. I believe that in 2015 we have made a successful start to this process of evolution, and I am confident that the journal will continue to progress in 2016.

At the beginning of 2014, I welcomed a group of internationally renowned leaders in their fields to form our new Associate Editorial team. Their dedication, hard work and continuing enthusiasm has been invaluable in moving *Annals of Oncology* towards our common goal of creating a modern, high-profile journal.

In addition, I am proud to announce that we have welcomed a number of new Associate Editors. Holbrook Kohrt, a cancer immunotherapy specialist working at Stanford, Dirk Arnold, an expert in the field of gastrointestinal cancers from the University Cancer Centre Hamburg, and Charles Ferté, an expert in digital medicine from Gustave Roussy Cancer Campus, have joined the team. This year we will also introduce new Associate Editors in melanoma, bioinformatics and gynecological cancers to further strengthen the team, in the persons of Georgia Long from the University of Sydney, Nicholas McGranahan from the Francis Crick Institute, and Bradley J. Monk from the University of Arizona. Each brings new expertise and ideas to the journal, adding value to an already first-class group of Associate Editors.

To encourage collaboration with industry, Kapil Dhingra, former Head of Roche Oncology and founder of KAPital Consulting LLC, has also been appointed to the Associate Editorial team. His contribution to the journal can already be seen through his coordination of the ‘Industry corner: perspectives and controversies’ series of articles. As well as welcoming our new team members, we must say goodbye to Caroline Robert and Mauro Delorenzi, who will leave the team in 2016. I would like to thank them for their hard work and contributions to the ongoing development of *Annals of Oncology*.

One of the major aims for the new *Annals of Oncology* team was to increase the number of randomized trials, top-level studies and high-profile guidelines and reviews published in the journal, which we believe will raise the visibility of *Annals of Oncology* and increase its impact factor. Indeed, in 2015 we saw our impact factor rise to 7.040, consolidating our position as one of the most widely read and cited journals in oncology. This reflects the efforts of the previous Editor-in-Chief Jan Vermorken and his team of Associate Editors. I am confident that we can continue their good work. In 2016, we expect to see our impact factor increase further. I believe that we are on target to achieve our aim of raising the Impact Factor to 10 by 2017. In order to achieve this, we have increased our overall rejection rate which has now reached 87% of all submitted manuscripts, to ensure we publish only the highest quality papers.

Our aim to increase publications of high-profile studies, guidelines and reviews is evident when looking at the most viewed articles in the journal. The ESMO Updated Clinical Practice Guidelines [1] remain among our most viewed articles of 2015, along with recommendations for the evaluation of tumor-infiltrating lymphocytes (TILs) in breast cancer [2] and the St. Gallen consensus statements on breast [3] and prostate cancer [4]. In 2015, we have increased the number of original articles published in the fields of onco-immunology, precision medicine, bioinformatics and statistics. In addition, under the guidance of our associate editor Marc Buyse, we have introduced the ‘Statistical controversies in clinical research’ series of articles, which aims to involve oncologists in the debate surrounding new developments in clinical research methodology. For certain cancers, where few treatment options previously existed, progress in tumor immunotherapy has brought hope to many patients. Research in this field is thriving, not only with continuing clinical trials of existing and novel immunotherapy agents, but also with studies into applications of immunotherapy across different cancer types and into reducing the adverse effects of these agents. Understanding why immunotherapy can induce remarkable and durable responses for some patients, but not all, also continues to be an area of intense interest. With many heralding onco-immunology as the cornerstone of a new era of cancer medicine, I believe that *Annals of Oncology* is addressing the demand for papers on this topic, as illustrated by the appointment of an additional Associate Editor in the field, Holbrook Kohrt, to work alongside George Coulkos.

I strongly believe that the evolution of *Annals of Oncology* towards becoming a top-level journal is well underway. I would like to thank all those involved in this process, including the Editorial Board, our committed reviewers, and our authors and readers for helping us on the road to achieving this aim. I would also like to thank the *Annals of Oncology* Editorial Office staff members and Oxford University Press, who provide all the necessary support for the global cancer community and continuing our progress towards becoming the reference oncology journal.

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