Aron Goldhirsch: dogmatically anti-dogma

Marc Beishon

To find out what makes cancers tick and work out how best to treat them, oncology must continually reinvent itself, applying rigorous methodology to interpret the results of well-designed and accurately reported studies. So says Aron Goldhirsch, who has revelled in a career doing just that in breast cancer – possibly the most biologically complex cancer of all.

Controversy is one of the most devalued words in the oncologist's lexicon – or at least it can appear that way to outsiders looking at what seem like tiny differences in treatment variations. But for an insight into just how deep these controversies can actually lie, look no further than the St Gallen international expert consensus conferences and their influential breast cancer recommendations, and one of their equally influential organisers, Aron Goldhirsch.

The St Gallen conferences are now held every two years, with this year marking the 10th meeting at the main town in eastern Switzerland. Their focus is on the treatment of primary breast cancer and especially on adjuvant treatment, reporting and discussing some of the most pivotal topics in oncology, such as the trials of Herceptin (trastuzumab). The 4,500 delegates to the 2007 meeting not only have the chance to hear probably one of the best assemblies of top breast oncologists worldwide, but also to put them on the spot about a field which has moved very fast in the last few years and which generates enormous hype in the media.

In Goldhirsch, breast oncology has a professional with, according to close colleagues, a fierce ability to cut through such hype. In a career stretching back over 30 years in medical oncology, and breast in particular, he has gained a reputation for a constant search for new biological knowledge to apply to clinical practice and research – but balanced by a forensic ability and an encyclopaedic knowledge of the literature to rapidly knock down any results that are not reported with due rigour – as is all too frequently the case, in his view.

He is concerned about issues such as rushing into practice without adequate follow-up data, misleading presentation of results of the trade-off between benefit and harm in new treatments, and especially the pharmaceutical industry's involvement in controlling trials. "Tailoring therapies to prevent metastases in a million women a year around the world is big business – the way that results of trials are reported can change the entire interpretation," he says.

Such is the degree of tension between academia and industry that Goldhirsch and colleagues are this year aiming to elevate the issue to wider debate

ELIGIO PAONI / CONTRASTO

beyond oncology circles by submitting a paper to *Nature* on the importance of maintaining academic independence in conducting clinical trails. "We want to start a political discussion. By taking a major field such as adjuvant therapy in breast cancer we want to help people understand the methodology behind our research, and we hope then researchers in other diseases will follow our lead."

The research Goldhirsch refers to includes the large-scale adjuvant breast cancer work organised by groups such as the International Breast Cancer Study Group and the overarching organisation, the Breast International Group (BIG), both of which he has played a major role in since their inception.

International work occupies a large amount of his time outside of his two primary employed positions – he has the unusual arrangement of a two-day-week post at the Oncology Institute of Southern Switzerland, as head of medical oncology, and three days a week across the border in Italy at the European Institute of Oncology in Milan, where he is director responsible for the medical area, including care and research in medical oncology, haemato-oncology, new drugs, supportive care and palliation.

"The principle of academic freedom is especially important to our adjuvant research, as it is all about giving treatment to women who are free of disease so you cannot check for efficacy and benefit," says Goldhirsch. "But it is like insurance. Someone will always sell you insurance for any calamity in the world. But what is reasonable in breast cancer concerns the characteristics and risk of the disease and targeting only what is important – and leaving aside what is not important."

It is a point that goes to heart of his concern for the development of oncology as whole – it is often easier to give more treatment than is necessary based on what works on average rather than thinking more deeply about the characteristics of the individual patient – and this is precisely where Goldhirsch intends the St Gallen conferences to make an impact.

Goldhirsch's parents were among the few from his family to escape the Holocaust – he was born in a Jewish refugee hospital in Germany in 1946. Two years later, his family moved to Israel, where he lived until the age of 21. He wanted to become a veterinary surgeon,

"Tailoring therapies to prevent metastases in a million women a year around the world is big business"

inspired by an uncle who was in this field, but he ended up turning to human medicine, finishing his initial training at medical school in Milan. His interests at this stage lay in infectious diseases, and indeed he planned to become a gastroenterologist.

"I applied for a Green Card to go and work in America, and while waiting I went to Switzerland – and never left after all." He had met oncologist Franco Cavalli, who had designs on establishing a centre of excellence in southern Switzerland, and persuaded Goldhirsch to make the switch to cancer. "At first I wasn't interested at all," says Goldhirsch. Nevertheless, he first joined Cavalli as the only other cancer physician in Bellinzona, but did his main formative years in internal medicine and medical oncology in a 10-year spell in Berne from 1978 to 1988, before returning to help build what was to become the Oncology Institute of Southern Switzerland, one of Europe's pioneering multidisciplinary centres.

"The features of medical oncology that attracted me were the methodology and the lack of dogma – the fact that whatever we have developed for the patient today will almost certainly be obsolete in the future. It is true that there was a lot of dogma around in the 1980s – and there still is in some places – in that the ideas of how to kill cancer cells were far away from the reality of their biology. It has taken many years and a lot of effort by those not immersed in dogma to convince others that new methods must be found."

His interest in breast oncology arose once he saw that cancer was a wide set of diseases and it was clear that breast offered the highest volume and widest spectrum of disease in itself. "There is such a large spectrum of biological features – why do a 20-year-old and an 80-year-old die within a year, and a 25-year-old live for 35 years with the disease? And there is a huge human dimension in terms of women's personal lives. All the features of the disease, the treatments and the patients, and their interaction, means that each factor needs a lot of attention – and for an oncologist there must be a synthesis somewhere that you can summarise for the patient. I was fascinated by the complexity."

In Berne, Goldhirsch soon found himself involved as a young clinician with what was to become the International Breast Cancer Study Group (IBCSG – it was a breakaway group set up by Jan Stjernsward of the Lausanne branch of the Ludwig Institute for Cancer Research), where he met his closest long-term collaborators and good friends, biostatistician Richard Gelber and medical oncologist Alan Coates, who have worked with Goldhirsch on many clinical trials and papers, and on the St Gallen consensus meetings.

FIGHTING FOR ACADEMIC INDEPENDENCE

Goldhirsch and colleagues hope to make an impact this year with a short paper in *Nature* on 'the essential role of academic independence' in early breast cancer clinical trials. They note that falling mortality rates in many countries are the direct result of such trials, and highlight the implicit ethical contract between researchers and patients. The nature of adjuvant trials is crucial – studies need to be large scale to explore often small differences in outcomes, and should increasingly be tailored to certain groups and followed up properly.

This all requires a lot of resources, but they are concerned about conflicts of interest, particularly between investigators and pharmaceutical companies. While recognising that commercial success for industry is necessary, they feel that the interests of patients may not be served best if a number of issues are not addressed. These include the need to secure funding for translational work and follow-up beyond commercial implementation, data being controlled or suppressed by industry, and trial questions and design being skewed to commercial interests.

For these reasons, the authors ideally would like large-scale trials to remain in open research networks such as the IBCSG and, for global collaboration, the BIG.

Another big issue driving Goldhirsch and colleagues to print is, of course, the overall regulatory constraints on clinical research, of which industry involvement is just one part. Increased bureaucracy, the cost of drugs, lack of healthcare cover for trial participants and disparate insurance requirements in some countries are all factors that "have made it almost impossible to conduct academically independent clinical research," according to another paper written by Goldhirsch and colleague Alan Coates.

BIG prize winners. Martine Piccart and Aron Goldhirsch co-chair the Breast International Group. They are pictured here at last year's ESMO conference, Istanbul, where BIG was presented with the Lifetime Achievement Award in Targeted Therapies in Cancer Research and Treatment

The forerunner to the IBCSG, the Ludwig Breast Cancer Study Group, was specifically established to run large-scale, international trials of the then very new field of adjuvant chemotherapy and endocrine therapy (and it's said that the designs for the first trials were written on a napkin in a hotel in Lausanne). "The trials were the first of their type in the world," says Goldhirsch. "They were also among the largest trials for any cancer at the time for the type of questions we were asking. We could not involve all the countries we wanted to in the early years, but now the IBCSG is working in countries such as China, India and Nigeria – our aim is to give as many women as possible at least the chance to be offered the opportunity to enrol in clinical research."

Goldhirsch says there are three main areas that have been brought forward from this work on early-stage breast cancer. "The first is that women may need a combination of chemotherapy and endocrine therapy to try and reduce the risk of relapse. Then by studying the biology of the disease you might understand why one treatment, both or none might be the priority. And third, we introduced quality of life measurement into the adjuvant setting. We wanted to quantify this, as we must not forget that adjuvant treatment is given to well women, free of disease after surgery and being treated to prevent relapse. Not all will relapse and to find out who benefits most from treatment is the big challenge and is where the study of endocrine response and non-response comes in. It was the early days of targeted therapies, which we were pioneering in."

Quality of life issues concern Goldhirsch greatly. He helped Richard Gelber, of the Dana-Farber Cancer Institute in the US, develop Q-TWiST – Quality-adjusted Time Without Symptoms or Toxicity – which aims to produce a single measure that integrates both quality and quantity of life. It is still in evolution in evaluating trials, he says, but adds that he is concerned that what he calls 'market forces' – the powers behind many trials – do not routinely report the quality side of the trade-off.

"The features of medical oncology that attracted me were the methodology and the lack of dogma"

"The language of two- or five-year survival is a notion you need to know, but it's often given the importance it does not have and greatly irritates me," he says.

It is an issue that has very much crossed over to clinical practice during his career. As he explains, with Franco Cavalli he helped develop what he calls an interdisciplinary model for cancer care in southern Switzerland, the distinction being with multidisciplinary working in a more narrow setting of, for example, tumour boards. Interdisciplinary working is, he says, about a much wider understanding of the patient's journey and experience as well as new drugs and treatments.

This can mean networking with colleagues in remote referral centres, working with disciplines outside of oncology, developing expertise in palliative care, especially when working with new drugs, and in general being able to understand how all the issues surrounding the patient shape their personal experience.

"Most medical oncologists don't have this ethos and their weaknesses relate mainly to knowledge of other problems," says Goldhirsch. "We must understand that a person who by chance has a disease may have several other problems that must be approached systematically. There is a tendency to put the malignant diseases ahead of all the other medical and social problems, not least where payment is linked to medical oncology treatment. You can't see a tumour as unrelated to a person."

As a simple example, he says he remembers well a woman with metastatic disease with no other symptoms other than suffering greatly from an ingrowing toenail, which he treated himself. "The oncology surgeon didn't know what to do," he says.

Goldhirsch chairs a weekly meeting every Thursday at the European Institute of Oncology where upwards of 70 patients are discussed in three hours, attended by as many as 50 people from both the institute and other hospitals in the region. He says his style is to pose a lot of questions about the context of the patient – where they live, for example – and he imparts often offbeat related knowledge, to keep minds as focused on patient 70 as patient one.

"I forbid discussion on patients in the café or hallway, because that's unprepared and unstructured. At the meetings, all disciplines involved discuss the patients, and senior oncologists are responsible for recording the discussion." It's a meeting not to be missed by local oncologists.

"My work at the European Institute of Oncology is a highlight of my professional life," Goldhirsch says. He gives a special mention to Umberto Veronesi, director of the Institute, who in 1996 gave him the opportunity to lead medicine at the newly created institution, which emphasises innovation in patient care. "Umberto Veronesi's research over decades changed much of the surgical and radiotherapy approach in caring for women with breast cancer, allowing minimal damage to normal tissue while still efficiently treating the disease. This is a challenge for medical therapies too."

Interaction with several colleagues at the Institute has become extremely intensive on these specific lines. "Giuseppe Viale and his team of pathologists are at the forefront of our translational research and provide continuous clinical guidance on how to better define and report on features that help prediction of prognosis and responsiveness to therapies."

It is the latter issue – defining which tumours respond to which therapies – that has been assuming centre stage in the St Gallen conferences, and looks set to do so again this year. The conference is the brainchild of Hans-Jörg Senn of the St Gallen Tumour Detection and Prevention Centre, and Goldhirsch has been one of the main contributors to the scientific part of the programme.

The need to discuss controversial issues at St Gallen was mooted with Richard Gelber and other famous cancer specialists such as oncologist John Glick and surgeon Bill Wood, says Goldhirsch, evolving from its initial purpose of a gathering of clinical trialists. Since the third meeting, the expert consensus has been in operation, and its recom-

mendations – not guidelines – have become increasingly cited in the literature.

"Guidelines are important as they confer regulatory and payment responsibility, and put order on what can and cannot be done in oncology, as the spectrum of abuse in diagnostics and therapeutics can be huge," says Goldhirsch, adding wryly that changing a payment regime can be the fastest way to change the behaviour of medical oncologists. "The St Gallen consensus is a set of recommendations on areas of grey – commonsense judgements from experts of what to do in controversial areas. We are trying to help people improve their understanding of the features of disease and not restrict themselves to dogma."

The main trend at the last few St Gallen meetings, says Goldhirsch, is a move "away from risk of relapse as the main treatment criterion to treating features of disease. We are now recommending treating first according to endocrine response and non-endocrine response, and we also define a group where endocrine response is uncertain." Categories of risk of relapse are at a secondary level – just a few years ago risk, based on the nodal status of the tumour, was the first category for consideration.

Such has been the accumulation of new evidence on adjuvant therapy since the St Gallen meeting of 2005 that Goldhirsch and colleagues issued an update last year under the title 'First – select the target…' (*Annals of Oncology* 2006).

One of the main reasons why St Gallen is an expert consensus, says Goldhirsch, is that they are making recommendations based on indirect evidence from population groups in trials, ideally after sufficient follow-up time. "When several subgroup analyses show the same direction it starts to be good evidence, such as avoiding chemotherapy in women in a high-risk group whose disease shows a huge endocrine responsiveness."

Goldhirsch is quick to dispel the notion that St Gallen is a club of like-minded oncologists, mentioning that among the experts there are several oncologists with whom he is in disagreement about several controversial areas.

The consensus can no doubt be hard to reach and the term 'robust debate' may well be an understatement. Goldhirsch is said to step up to such debate – as a colleague says, "Others may not suffer fools gladly: Aron is apt to destroy them comprehensively. It must irritate his opponents that he is so often proved right."

Goldhirsch is also among the strong critics of the presentation and interpretation of trials that are considered for evidence, mentioning the recent push to use aromatase inhibitors instead of tamoxifen as adjuvant medication. He says that their side-effects and cost are major factors, and while they are proven to better prevent relapse and death in women at high risk, long-term efficacy, a strong feature of tamoxifen effects, is still to be demonstrated. The ATAC (Arimidex, Tamoxifen Alone or in Combination) study, one of the largest ever studies on postmenopausal women with early breast cancer, certainly led to a division of opinion in the oncology

ST GALLEN: AN INTERNATIONAL CONSENSUS

Although the word 'adjuvant' no longer appears in the title of the St Gallen conference – the term 'primary therapy' is used – the expert consensus panel that convenes after three days of presentations has focused on adjuvant therapies. The 2005 recommendations emphasised endocrine responsiveness and a modified risk classification, a major development from 2001 when the focus was on multiple categories of risk based on the nodal status of a tumour. "Prognosis per se was considered less relevant to treatment selection," a 2006 update reports.

Goldhirsch says that the key topics for this year's consensus discussion are as before – endocrine therapies for pre-and post-menopausal women, chemotherapy regimens, and trastuzumab – and in addition radiotherapy will have a higher profile. The core recommendations from 2005 boil down to a simple table of three endocrine categories versus three risk categories, and recommended therapies.

The St Gallen consensus is not of course the only such classification. One other, the US National Institutes of Health Consensus Development Conference on Adjuvant Therapy, has been compared with St Gallen by researchers who noted in 2002 that, despite looking at evidence from the same trials, the resulting recommendations from the two meetings (held three months apart then) were slightly different (Breast cancer consensus meetings: vive la difference? *Journal of Clinical Oncology* 2002).

The details are now history, but the writers considered that the make up of the panels was, not surprisingly, the key to the difference, with St Gallen being a group of international breast experts and the NIH panel being only American citizens from diverse medical fields and also the public.

Members of this year's St Gallen panel include John Glick, Martine Piccart, Alan Coates and Richard Gelber – 37 in total – with Goldhirsch and Bill Wood in the chair.

Frontiers men. Aron Goldhirsch and Richard Gelber, president and vice president of the clinical/translational research support organisation Frontier Southern Europe, taking advantage of a photo opportunity

community, and it is notable that despite pressure to report otherwise, the latest St Gallen advice simply concludes: "Much less information is available on the long-term safety of aromatase inhibitors than for tamoxifen."

He expresses disappointment at the presentation of the pivotal Herceptin trials in 2005 in the *New England Journal of Medicine*. His group's results – the BIG Herceptin Adjuvant (HERA) trial, led by another of his close collaborators, Martine Piccart of the Jules Bordet Institute in Brussels – has graphs with disease-free survival plotted from 0 to 100%, whereas the joint American trials evaluation results were presented with plots truncated at the 50th percentile (50% to 100%) giving an entirely different graphical impression. "And that's the same journal, the same editors," he notes.

Goldhirsch says he's always pleased when the St Gallen recommendations are picked up by other researchers – an important recent example being their use as a benchmark for the new work on gene profiling in breast cancer, although he notes that "the majority of genes are related to endocrine and non-endocrine response," and that the information could probably be obtained at less cost with other means. However, he is a participant in the TRANSBIG MINDACT (Microarray In Node-negative Disease may Avoid ChemoTherapy) gene profiling trial, but only after he insisted that it was extended to cover node-positive as well as node-negative women to widen its value.

He feels St Gallen also offers better guidance for professionals than tools such as Adjuvant! Online (www.adjuvantonline.com). If nothing else, the meeting is for Goldhirsch a crucial educational exercise, and the opening state-of-the-art progress reports are well worth the trip.

But for breast cancer professionals in Europe, he considers there is still a missing piece of the conference jigsaw. St Gallen is providing state-of-

He would welcome more problem-based learning, particularly where it involves talking with patients

the-art recommendations; there is the Milan Breast Cancer Conference on Innovation in Patient Care; and the big European Breast Cancer Conference (next in Berlin in 2008) is a meeting of all professionals and, increasingly, advocate groups. "What's missing is a meeting on translational research just for breast cancer," he notes, adding that plans are already afoot to plug this gap. "I think our profession lacks a methodology to continually reinvent itself – we need all these four conferences to give us the right tools."

Goldhirsch has avoided most senior committee positions offered to him outside of breast cancer, but one post he did occupy for 10 years was president of the prestigious Swiss Group for Clinical Cancer Research (known as SAKK). His involvement came to an abrupt end in 2004 when he resigned after conservative rules were introduced in Switzerland that he says curtailed opportunities to carry out clinical research. He is now president of the recently established Frontier Southern Europe (www.frontier-se.org), based on the model and principles of the Frontier Science and Technology Research Foundation, its famous parent organisation, which was set up in Boston in 1975 to support trials of early cooperative groups such as the American Eastern Cooperative Oncology Group (ECOG).

If he could make one change now it would be in the training of medical students, and he would certainly welcome the widespread implementation of problem-based learning, particularly where it involves talking with patients. "Who teaches skills such as negotiation with patients?" he asks. Well, he and his colleagues go some way towards this aim at Milan – "We have developed a methodology for communication with various patient groups. Approaching, say, an older woman who may have a high chance of relapse is more efficient when issues specifically related to her needs are taken into account." Teaching professionals what they need for actually carrying out adjuvant treatment (or not) is not really being taught anywhere, he reckons.

Goldhirsch's own research interests, not surprisingly, home in on the cutting edge – the endocrine responsiveness of breast cancer in selecting the appropriate adjuvant therapy. He has, though, a particular interest in younger and older women – typically the 20–30- and 70–80-year-olds, who he feels are still neglected populations, despite breast cancer being such a large field. He mentions two important IBCSG studies that are addressing premenopausal women – Suppression of Ovarian Function Trial (SOFT) and Tamoxifen and Exemestane Trial (TEXT), but if there is one wish he has for a major trial he'd like to see through in his career, it would be a more specific study aimed at younger women.

That would naturally be another major international collaboration, and it is fitting that of all the awards he has received in his career, it is an honorary doctorate from the University of Gothenburg for his international work that he is most proud of.

Goldhirsch, who is now a Swiss national, lives in Switzerland with his wife, Francesca, an ophthalmologist, and three children who keep him on his toes with the latest pop music (although the 'Hot Red Chili Peppers' isn't quite what they're called). A big hobby is photography, and his main reading interest is science fiction, which is apt given his philosophy of doing away with dogma wherever necessary in medicine.

Given that the field of breast cancer has undergone a huge knowledge explosion, even Goldhirsch recognises that it is not possible to know everything, and indeed he foresees a time when it may need to be divided into sub-specialties – but without losing vital cross-fertilisation among professionals.

And there lies an increasing challenge for oncologists, who Goldhirsch would like to see abandoning dogma and participating in cultural – and political – changes to improve attitudes to care and research he feels are needed to apply new knowledge to best effect.