

Where East meets West

→ Peter McIntyre

The fall of the Iron Curtain offered European oncology the chance to swell its ranks with new cadres, keen to learn and bursting with ideas and confidence. **Christoph Zielinski**, born of Polish emigrés and raised in post-war Austria, grasped the opportunity. He set about building Central Europe into a centre of academic gravitation, and is now calling for a European ASCO.

Christoph Zielinski vividly remembers two moments during his presentation to the American Society of Clinical Oncology (ASCO) in Chicago in June 2003. The first was the chairman stumbling over the names of the authors as he introduced the multicentre paper on metastatic breast cancer. Besides Zielinski, he had to cope with Wiltschke, Beslija, Tzekova, Gric, Mrcic, Petruzelka, Szanto, Inbar, Krzakowski, Ghilezan, Korec, Koza, Zwitter and Onat – names that did not trip easily off his tongue.

The second came as Zielinski looked over the sea of faces and picked out authors from Bosnia, Bulgaria, Croatia, the Czech Republic, Hungary, Poland, Romania, Slovakia and Slovenia. “It was wonderful to see in the audience these people co-authoring a paper for ASCO. It was the most incredible thing that nobody believed would ever happen.”

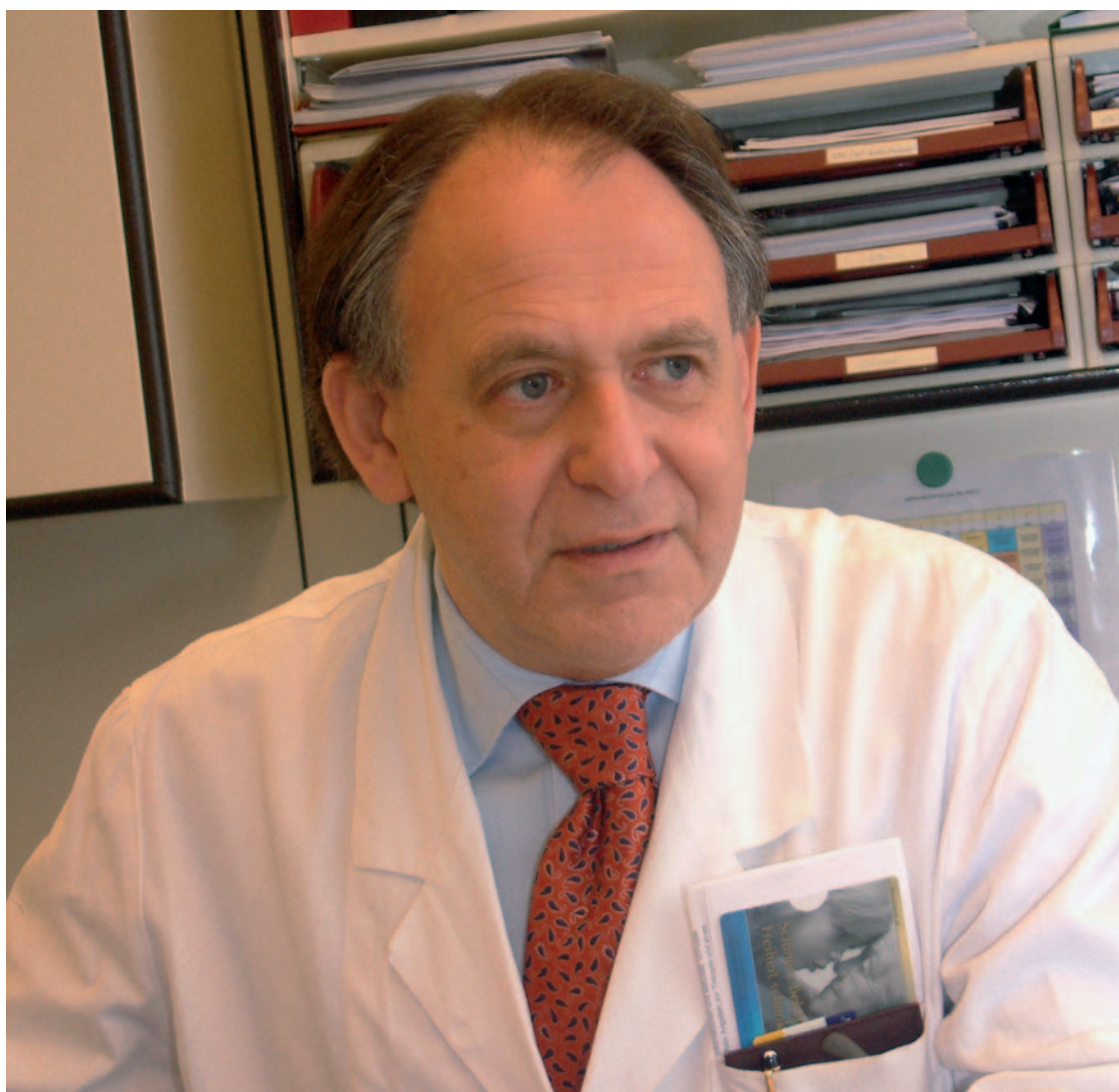
This was a report of the first multicentre trial carried out by the Central European Cooperative Oncology Group, a group built by Zielinski from his base in Vienna, drawing on his roots in Poland. Today CECOG is an established part of the global

oncology scene with a growing reputation.

This early research compared a chemotherapy regime of gemcitabine, epirubicin and paclitaxel (GET) to the established 5-fluorouracil, epirubicin and cyclophosphamide (FEC) as a first-line treatment for women with metastatic breast cancer, reporting on results in 259 women recruited from 29 centres.

The results were not spectacular. Although GET showed a higher response rate, there was a similar time to disease progression and, overall, GET was not superior to FEC. However, when the results were published in the *Journal of Clinical Oncology* in 2005, it marked an historic development in Central European research.

Zielinski has been uniquely placed as director of clinical oncology at the University Hospital of Vienna to build CECOG. Since the Austrian and Austro-Hungarian empires, Austria has been a gateway between Central and Western Europe, and continued this role after World War II. In 1938, Austria had been declared part of Germany under Hitler’s ‘anschluss’ (extension) policy. Following the war, Austria was under four-power control (US,



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Britain, France and USSR) until 1955 and did not join the European Union until 1995. In the post-war years it also became home to many of those who left the Eastern Bloc countries of Central and Eastern Europe, including Zielinski's own family.

Christoph Zielinski was born in Poland in May 1952, his father a businessman, his mother a university lecturer in Polish literature. In 1956, during a short period of relaxation by the Polish Communist Party, his family moved to Austria. Christoph grew up as a child of Vienna who spoke Polish at home.

His background has made him acutely aware of the isolation that researchers and doctors experience in politically repressive regimes. Throughout

his career, he has sought to make connections – between clinicians in North America and Europe, and across Europe. In the late 1970s, the US became a scientific lifeline. Today, he seeks ways to break down geographical hierarchies. He supports the building of a European alternative to ASCO and is strongly opposed to a two-tier Europe.

Zielinski became a doctor under the influence of family friends. On graduation in 1976 he began his specialist training alongside one of them, Martha Eibl, at the Institute of Immunology in the University of Vienna. “At that time, immunology was the science to follow. The difference between T and B cells had recently been discovered, but we did not know a

lot about T helper cells. It was the most fascinating area to work in, like molecular science today.”

Eibl stimulated his interest in clinical treatment as well as in research. “In the first two and a half years I was working only with mice and rabbits but she brought me to the clinical aspects, which ultimately got me started in the department of medicine here.”

SCIENTIFIC CLAUSTROPHOBIA

Even then, more than 30 years after the end of World War II, he found Austria scientifically claustrophobic, still in denial over its past. In 1938, 60% of Jewish teachers had been expelled from the universities in little more than six months. Those who did not leave met their deaths in concentration camps along with 60,000 of Austria’s 200,000 Jews and 10,000 Roma. Zielinski, a leading figure in bringing this ‘terrible past’ into open discussion, says that post-war Austria was still hostage to this legacy. “The Nazis put in their own followers as teachers, and usually people who are not that well qualified have pupils who are not that well qualified either. That was a brain-drain from which Austria, in my view, did not recuperate until the 1980s.”

In 1979, Zielinski was in the first wave of post-war Austrian researchers to look to America to break out of their isolation. “I went to Boston at the Cancer Research Center with Bob [Robert] Schwartz who today is an associate editor of the NEJM and one the most impressive men I have ever met in my life. It was hothouse atmosphere, because there was hardly a week went by but a Nobel Prize winner would give a talk or lecture.”

For two years at Boston he worked on leukemias and on bone marrow transplant rejection issues. “It was the most incredible time. I was in my late 20s and I was sort of adopted by Bob Schwartz and spent a lot of time at his house. I became involved in work on viral leukogenesis, which was enormously visionary on the part of the laboratory because HIV was still unknown and the T-cell leukaemia virus was still unknown.”

On his return to Vienna, he was drawn towards oncology. “I was doing a lot of testicular cancer at a time when treatment with cisplatin was being developed. It was effective, but there were no supportive drugs. Even today, when I see a patient getting platinum-based chemo, I wonder why he

isn’t vomiting – he is getting wonderful anti-emetic drugs. In those days, these poor guys were vomiting their souls out.”

He kept contact with some of his colleagues from the US, including Richard Margolese, today director of oncology at the Jewish General Hospital at McGill, Montreal, and a member of the CECOG advisory board.

However, it was two leading breast surgeons in Europe who inspired Zielinski to look east. Umberto Veronesi and Alberto Costa were two of the founders of the European School of Oncology established to bring better practice and techniques into widespread use, under the motto ‘learning to care’. Zielinski recalls: “They were the other influencing forces on my clinical development, and they were enormously academically orientated as practising clinicians.”

ESO was looking to expand clinical training to a greater number of countries, and in 1989 Zielinski became the first chairman of ESO’s Central European Office in Vienna.

“We established a scientific committee recruited from the most well-known people from these countries. We also established a faculty, the majority from the West. We wanted to transfer information, to bring them up to a similar level. We decided to teach basic information about clinical trials and about treatment of certain malignant diseases.

“These guys had been living behind the Iron Curtain for 60 years and were enormously isolated. This is a parallel with what happened in Austria. They were political victims and denied information or access to additional drugs. The few who were allowed to visit conferences were selected not by virtue but by political context.”

There was a huge appetite for knowledge and an enthusiasm for the courses. The only problem was the lack of debate after lectures, reflecting decades of being told to accept official information. That deference has long since gone, and meetings in Central Europe today are very lively affairs. ESO ran more than 50 courses for oncologists from Central Europe and the headquarters in Vienna hosted more than 1,000 visits from the region. However, after ten years’ work ESO judged that the needs of clinicians in the region were now so similar to those in Western Europe that it was no longer appropriate to separate clinical education. The

Central European office closed and ESO training became Europe wide.

In 1999, Zielinski founded the Central European Cooperative Oncology Group, using the contacts he had made through ESO. "Having been educated by the European School we wanted to perform trials together and generate a centre of academic gravitation in Central Europe." Today CECOG collaborates with 120 academic centres in 16 countries.

BURSTING WITH IDEAS

Zielinski found himself at the hub of a group bursting with ideas. "It is funny what happens in life. For 40 years my Polish was an unnecessary luxury because it was not spoken except inside Poland.

Suddenly, it turned out that speaking Polish was important because I could speak to all these people, or at least understand colleagues from the Czech Republic, Slovakia, Croatia, Bosnia and Slovenia."

The geography is sometimes unorthodox. CECOG includes centres in Greece and Cyprus, and works with researchers from Israel, Portugal and, from time to time, South Africa. "This is a classic Central European approach," says Zielinski cheerfully.

Leaving aside the outliers, CECOG countries have similar economic backgrounds and common characteristics. "First they have a common past which unites them, going back to the Austro-Hungarian empire. Then they have this common tragic history of Communist rule for 60 years, so a common sense of isolation. Third, there is a common feeling that they are getting better. They are motivated to recruit patients to trials and to deliver the best care. There is no trace of saturation, which we often find in the West."

CECOG has largely focused on multicentre trials for patients with advanced lung cancer and



Negotiating access. Zielinski helped convince the Vienna City administration to fund all the latest cancer drugs for a consortium of seven hospitals in the city. He is pictured here with Vienna City Councillor Renate Brauner in 2005

metastatic breast cancer, reflecting the reality of disease in many of these countries.

In 2006, CECOG published a paper in *Lung Cancer* on the use of gemcitabine (Gemzar) as a maintenance drug in patients with advanced non-small-cell lung cancer. This showed a modest but significant increase in time to progression from 5 months with best supportive care to 6.6 months with gemcitabine. Benefits were most marked in patients with a good performance status, and the research has led to new treatment standards.

This paper was authored by 20 researchers from Central Europe. Zielinski says, "They not only included their patients in a trial, but were very much involved in the design, the acceptance of the trial, its performance and follow up. That was a major step forward for Central European oncology."

CECOG is participating in a multicentre trial of pemetrexed (Alimta) as maintenance therapy for patients with advanced non-small-cell cancer, and is planning a trial using bevacizumab (Avastin) in metastatic breast cancer. The results of a trial

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on treatment of advanced colorectal cancer will be presented at the ECCO conference in Barcelona later this year. Publication is also being prepared of a trial of gemcitabine plus capecitabine in patients with advanced pancreatic cancer. Other areas being investigated include comparisons between concomitant and sequential therapy in breast cancer – a controversial topic, according to Zielinski, “that has led to the end of friendships!”

CECOG has a scientific committee made up of oncologists from Central Europe, and an advisory board composed of eminent members from the region, such as Jacek Jassem from Gdansk, Poland, and from the West, including Martine Piccart and Gordon McVie. The scientific committee designs protocols for the research projects, while the advisory board helps to spread information in the West.

CECOG has published consensus guidelines on treatment of non-small-cell lung cancer and on metastatic breast cancer, the latest of which is set to be presented by Zielinski at the 1st Interconference Breast Cancer Meeting in Sarajevo in April 2007. A consensus statement on colorectal cancer will be agreed on July 5 and 6 this year.

MINIMUM QUALITY

“One thing that unites these countries is limited resources, and we wanted to define the minimum quality required to fulfil all criteria of appropriate quality treatment for patients. There are a lot of guidelines about adjuvant treatment of breast cancer but almost none on the treatment of metastatic breast cancer. They were closely watched and very well accepted.”

Zielinski has now stepped down as coordinator of CECOG, a role that has been taken over by Thomas Brodowicz, his colleague in Vienna. Now, as president of CECOG, Zielinski sees his role as finding organisations who want to collaborate. “Over the course of time CECOG has grown enormously and we have our own offices and employees outside

the hospital. There are lots of things to do. We try to talk industry into supporting trials that interest us academically and are of interest for the industry.”

This work comes on top of his day-to-day role as director of clinical oncology and coordinating director of a department of medicine that covers oncology, haematology and infectious diseases at the University Hospital. There are 112 in-patient beds with additional beds for palliative care, intensive care and bone marrow transplantation, and 100,000 patient contacts a year. Oncology delivers 6,500 to 7,000 outpatient chemotherapy treatments a year.

As professor of oncology Zielinski also has a heavy workload of teaching, research and administration. He is proud of the fact that in 2006 the department achieved ISO quality certification. To that can be added 310 or so peer reviewed research papers, participation in more than 50 academic books, editorship of *Onkologie heute* and editing of translational research for *The Breast*.

In moving “from eminence-based to evidence-based medicine”, Zielinski says that it is crucial to keep up to date. “I consider translational research as the major challenge – not only from bench to bedside, but also from bedside to bench. We have recently integrated the cancer research clinic into our department, as it is important for basic researchers in the laboratory to see the problems arising at the bedside.

“We tell basic researchers about problems, and ask what they think. For example, we ask them about the acneiform rash that occurs when you give EGFR inhibitors. Why does this happen and could this be a surrogate parameter? We are only at the beginning. I want to combine a closer collaboration with rapid access to promising drugs. The vision I have is a benefit for the patient and for the clinic.”

This also has implications for teaching. “The world used to be much more stable than it is now. Thirty years ago we were taught everlasting eternal truths. Now we teach state of the art, in which the state and art change very quickly.”



Fund raiser. Funding for cancer drugs in Austria is good, but of EU countries, only Bulgaria, Latvia, Romania and Poland put less money per capita towards cancer research. Zielinski is seen here thanking the Vienna Philharmonic Orchestra, which holds an annual concert to raise funds

In Europe, Austria comes second only to France in the EORTC assessment of life expectancy for cancer patients, and was praised by the Karolinska pan-European report on patient access to cancer drugs. The city administration of Vienna recently agreed with a consortium of seven hospitals to fund all the latest cancer drugs. However, even in Austria the economics are challenging. The country is predicting a sixfold rise in the number of people over the age of 90 in a few decades.

Another innovative step is to attempt to improve public understanding by running workshops for journalists. “Journalists continue to write about how stress will change your immune forces and enhance the development of cancer. It is very difficult to explain to them what a complex area this is and how many things have to happen before a cell becomes malignant. We are trying to develop some experience here and will have the first workshop after ASCO this year.”

A EUROPEAN ASCO

Zielinski sees a strong connection between political and scientific development. When politics fail—as in Austria in 1938 and in post-war Warsaw Pact countries—science and medicine become distorted and

stultified. Today, he believes it is essential to develop a European scientific conference that can equal ASCO. “I am very sad that somehow Europe still does not manage to have ASCO. I don’t know why, but even Europeans present their most important results at ASCO. That is a sad story because I think that Europeans should be more self-assured.”

He is disappointed with the way that the US, once his lifeline, now conducts its international relations. “It is not that I want to criticise anything, but when we were going to ASCO last year in Atlanta, I could see all the guys who are the most eminent partners of the CECOG, very eminent oncologists, standing in the immigration line for two and a half or three hours. The degree of humiliation is enormous when we go to the States.”

But Europe too has its first- and second-class citizens. “We have generated a European Union which is not a union. You can go from Vienna to Paris without a passport, but when you go from Poland or the Czech Republic you pass a border control, and they are not allowed to work here except for certain very few exemptions. They are proud of being integrated into Europe, but they feel this discrimination very often.

“This irritates me a lot. Austria is one of the classic winners of the opening of the European Union to the East. But still there is a lot of opposition to people coming in, because people are afraid they will lose their jobs. Nobody has seen this enormous opportunity to go and get jobs there.

“If I were 30 years old today, I would learn Polish and apply for a job as a chief of oncology in Krakow or Warsaw or Prague. In 30 years these will be the thriving cities. Of course, there are a lot of people who have lost their identity and who are losers. If politics was not so preoccupied with itself in these countries, it would look for these losers and help them to integrate into this new system.”

Looking for the people who lost out and helping them to break out of isolation is one of the themes of Zielinski’s career, but even so he refuses to take himself too seriously. “When you are living in a small country like Austria you have two choices. Choice number one is that you remain part of the small local community and you are, as Caesar said, ‘first in Gallia’. I prefer to be the second in Rome! It is more fun to be internationally connected and it leads you out of your small horizons.”