Plenary Session

ESTRO Award Lecture

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Towards prediction and modulation of treatment response

H. Bartelink. *The Netherlands Cancer Institute/Antoni van Leeuwenhoek Huis, Amsterdam, The Netherlands*

A new generation of molecular biology assays and developments in more conventional diagnostic tests are becoming available, providing us with much more knowledge on tumor characteristics and tumor response to therapy. This development offers new predictive assays leading to improved treatment outcome, through selection of a suitable treatment regimen for an individual patient. The avoidance of exposure of patients to unnecessary treatment and its toxicity will also be an added benefit of these assays. Insight into the mechanism responsible for the response to treatment, measured by these assays, will also guide us in the application of new treatment schedules and drugs. Modulation of the tumor response and its successful application in clinical practice now become possible. The purpose of this lecture is to present the development of new predictive assays and the positive impact in the clinic by profiting from the presently existing knowledge derived from clinical trials.

A first example is the development of a functional estrogen receptor assay (ER-FASAY) based on a yeast assay, which was developed in our institute. With this assay it is possible to detect the presence and (abnormal) functional activity of ER in breast tumors. Only 60% of all patients with ER-positive tumors, measured by immuno-histochemistry, will respond to hormonal therapy.

We anticipate that in the future, using the ER-FASAY, we will be able to establish a better correlation between ER-status and hormonal response. In this way, optimal use can be made from the outcome of an EORTC trial in locally advanced breast cancer in which we were able to demonstrate that adjuvant hormonotherapy resulted in a significant benefit in long term survival, while no effect was seen with adjuvant chemotherapy.

The measurement of the effect of drugs on DNA level, became possible for cisplatin with the development of antibodies against DNA-adducts. In the recently completed dose escalating phase II trial with concomitant radiotherapy and cisplatin in non small cell lung cancer, we discovered that patients in whom a high content of cisplatin DNA-adducts was measured in the buccal mucosa had a much better survival rate than patients with a low or not measurable amount of cisplatin DNA-adducts. These findings are in line with the results that cisplatin given daily concomitant with radiotherapy lead to a better local tumor control and survival compared with radiotherapy alone.

We expect that other assays which we have developed to predict the response to treatment by measuring tumor characteristics such as the growth potential with labeling index after i.v. injection of IUDR, the amount of stable and unstable chromosome aberrations and the induction of apoptosis, can lead us to adapt the individual treatment regimen and dose. The knowledge derived from these investigations into the mechanism of cell death suggests that drugs such as the alkylphospholipids should be tested in the clinic to increase apoptosis.

SIOP Award Lecture

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Improved results in pediatric oncology: More survivors, better survival, still much to do

Jean Lemerle. *Department of pediatric oncology, Institut Gustave-Rroussy, Villejuif, France*

Cancers of childhood are different from those seen in adults. The numbers are much smaller: 1 child under 15 for 100 adults, in Europe. The involved sites are not the same. In children, we see mostly leukemias, 30% of the cases, CNS tumors 20%, lymphomas (Hodgkins and NHL) 15% in Europe, tumors of the kidney, neuroblastomas, tumors of the soft tissues, of the bones, the liver, the retina, etc. represent 1 to 10% each. There are almost no tumors of the breast, the digestive tract, lungs, skin, uterus. There are very few carcinomas; leukemias and lymphomas represent 45% of the cases, embryonal tumors 35 to 40%, sarcomas and non embryonal brain tumors, 15 to 20%.

These major differences are linked with *different natural history*, very rapid growth and spread of children's tumors, correlated to an excellent response to radiotherapy and to most drugs, which resulted in an overall cure rate miltiplied by 3 in 25 years.

But improved results in terms of survival were partly spoiled by the occurrence of the *late adverse effects of the treatments* which arose progressively during all the growth period. Radiotherapy given to children can effect growth or function or both. The damage is correlated with dose, age at treatment, involved area, and can be fully assessed only when growth is completed. Chemotherapy has fewer long term effects, except anthracycline induced cardiotoxity, male infertility due to alkylating agents, lung or kidney impairment by several drugs. The drawbacks of otherwise very successful treatments became obvious, and rapidly unacceptable.

Strategies were develop worldwide aiming *at minimizing late effects while further improving cure rates.* Unnecessary treatments were cut, new drugs were tried, less aggressive radiotherapy techniques were used, and supportive care was improved, allowing more aggressive chemotherapy to be used. National and international large study groups were set up, all aiming at obtaining better quality of life and of survival, at a lower cost, with more selective treatments which tend to be individualised according to risk factors.

At this point we can say that, at least in specialised centers or study groups, 70% of children with malignancies (including leukemias) will be cured.

Solid tumors can be divided today into 3 groups, according to survival rate and treatment burden:

1) The very good cases (37% of solid tumors) are Wilm's tumors, Hodgkin's disease, NHL (mainly B cell type), and neuroblastomas except metastatic aged > 1yr. In all these cases, survival rate is 90% or more, treatments are short and selectively adapted, almost no sequelae at all are to be expected.

2) Good but more difficult cases (30%) are bone tumors and soft tissue sarcomas. Cure rates range from 65 to 80%. But treatments are still longer, often much more aggressive than in group 1, and severe sequelae are to be expected in a proportion of cases, despite our efforts to replace amputation by sophisticated surgery and radiotherapy by primary chemotherapy.

3) Unsolved problems (33%) are stage IV neuroblastomas (Nb) aged > 1 yr, and most brain tumors. Survival is poor in stage IV. Nb Despite very intensive chemotherapy including ABMT. Quality of survival is still very poor in brain tumors despite efforts made everywhere to develop new chemotherapy regimens.

Pediatric oncology has achieved a lot in 30 years, but there is still much to do for at least 50% of the patients who present with a tumor or a leukemia.