has not improved over the last 20 years. During this time the mainstay of treatment has been single agent chemotherapy, most often with dacarbazine although other alkylating agents, platinum based drugs and vinca alkaloids are also used. Immunotherapies hold some promise, yet phase II studies of interferon and interleukin 2 have not indicated better outcomes for this group of patients than with chemotherapy. A small minority of patients achieve durable complete responses with interleukin 2. Twice in recent years important advances in treatment appear to have been made, but on both occasions large scale studies have failed to confirm earlier results. In the 1980s phase II trials demonstrated greatly enhanced response rates for combination chemotherapy, particularly the Dartmouth regimen of dacarbazine, BCNU, cisplatin and tamoxifen. Multi-centre phase III trials confirmed this increase in responses, but found no impact upon overall survival. The initial, promising results are likely explained by patient selection, for within the grouping of metastatic melanoma there is a wide variation in survival time. The recent AJCC classification highlights this: 29% of patients with M1a disease will be alive at 2 years, compared with 7% with stage M1c. A similar story is being played out with biochemotherapy. Single institution phase II trials suggested a substantial benefit for this approach in patients able to tolerate treatment. Initial interest centred upon the combination of dacarbazine and interferon. However, an ECOG study involving over 250 patients found no advantage to this combination over chemotherapy alone, a finding borne out in a recent meta-analysis. Other groups have tested a variety of combination chemotherapies with varying regimes of interferon and interleukin 2. Phase III trials of the most promising biochemotherapies, involving hundreds of patients, have shown no survival advantage over chemotherapy alone. In 2003 the best treatment option that we can offer patients with metastatic melanoma, outside of clinical trials, is still single agent chemo- or immunotherapy.

350

Design and testing of chemically–defined melanoma vaccines

J.-C. Cerottini. *Ludwig Institute for Cancer Research, Lausanne Branch, Epalinges, Switzerland*

The molecular identification of melanoma antigens recognized by CD8 and CD4 T cells has paved the way to approaches for the design of therapeutic cancer vaccines that are based on the use of chemically defined antigenic peptides and adjuvants. Most of the trials in progress are focused on the vaccination of melanoma patients with peptides derived from cancer germline gene products, such as the MAGE family, and/or melanocyte lineage-associated proteins, such as the Melan-A/MART-1 antigen. The selection of the antigenic peptides to be incorporated in a given vaccine has to take into account the HLA allele pattern expressed by individual patients as well as the antigenic peptide profile of individual tumors. In some instances, the immunogenicity of peptides can be increased substantially by altering specific aminoacid residues at positions that anchor the peptide to the corresponding HLA molecule and/or confer susceptibility to proteolytic degradation by proteases. As the number of variables to be tested for the optimization of antigen-specific T cell responses is very large, the initial evaluation of vaccine-based strategies cannot rely on usual clinical end points, such as tumor regression or time to recurrence, because of the number of patients and years required to achieve meaningful results. Instead, immunological assays that enable quantitative and qualitative monitoring of antigenic peptide-specific T cell responses are being used to evaluate the immunogenicity of candidate vaccines in phase I clinical trials. Although monitoring methodologies have undergone considerable improvement over the past few years, the complexity of the immune response makes the identification of the most effective immunization procedures quite a challenge. Moreover, application of these assays to the monitoring of specific CD8 T cell responses induced by peptide-based vaccines in melanoma patients has revealed significant interindividual differences, which may reflect the preexistence, or lack thereof, of a spontaneous tumor antigen-induced response in these patients. It is thus necessary to use standardized assays to evaluate the development of immune responses triggered by different vaccine strategies in individual patients. In addition, immunological monitoring should include analyses both in the peripheral circulation and at the tumor site because of possible numerical and functional discrepancies between tumor antigen-specific T cells residing in these compartments

351

Conformal radiotherapy in prostate cancer: development of the new "standard of care"

D.P. Dearnaley. *The Royal Marsden Hospital, Department of Radiotherapy, Sutton, United Kingdom*

The last decade has seen the widespread implementation of CFRT and dose escalated treatments for prostate cancer. Large "phase I" studies, principally from specialist centres in the USA, have documented the safety of these techniques with reports of apparent improvements in disease control. However, it has recently been appreciated that cohort effects in sequentially treated groups of patients may have led to significant bias due to "stage migration". The results of single centre phase III dose escalation trials (MD Andersen and Institute of Cancer Research/Royal Marsden Hospital) indicate improvements in PSA control for men with advanced localised disease, but benefit for patients with good prognosis disease has not yet been confirmed. Assessment of other clinically meaningful endpoints such as metastases free and overall survival will become possible as other larger multicentre trials, which will in total recruit approximately 4,400 men, reach maturity. Data from these trials and other sources should more clearly define dose-volume-complication relationships and individualisation of treatment based on prognostic features for tumour control and complication probabilities may become realistic.

The role of IMRT is yet to be clearly defined but may offer advantages for some anatomic configurations; complex high dose volumes can be shaped and pelvic lymph node irradiation achieved with a significant reduction in bowel volumes treated to high dose. Modelling studies have shown the potential benefit of intra-prostatic boosts, but improvements in MRI and functional imaging are needed to define such "dominant intraprostatic lesions". Such refinements in treatment require attention to the details of all parts of the "technology chain" in particular to the verification of treatment accuracy taking into account the potential for prostate target movement. A variety of localising devices (fiducial markers, localising catheter, ultrasound, rectal balloons) are being assessed to enable development of guided radiotherapy techniques. These methods of "physical optimisation" will be complementary to "biological optimisation" approaches using both altered fractional or combined modality treatments.

352

Combination of hormonotherapy (HT) and external irradiation (RT) in prostate cancers. Neo-adjuvant and/ or adjuvant hormonotherapy?

M. Bolla. *Centre Hospitalier de Grenoble, Department of Radiotherapy, Grenoble, France*

Androgen suppression improves the outcome of external irradiation: it possibly eliminates occult systemic disease outside the irradiated volume and has at least an additive effect on local control by inducing apoptosis. RTOG and EORTC trials investigated this combination in locally advanced prostate cancer, cT2c-T4 N0-1 M0 (UICC 1992). Protocol 86-10compared androgen deprivation (flutamide and goserelin) with radiation therapy vs radiation therapy alone in patients with large T2 or T3-4 tumors; androgen deprivation was initiated 2 months prior to starting radiotherapy and stopped at the completion of radiotherapy. Hormonotherapy increased the local control, distant metastases free rate, progression free survival and overall survival in patients with Gleason score 2-6. Protocol 85-31 was devoted to adjuvant androgen suppression with goserelin in T1-2 patients with regional lymph node involvement, T3 regardless of regional lymph node status or pT3 after prostatectomy. Goserelin was started at the end of the radiotherapy and continued indefinitely. There was an increase of the local control, distant metastases free rate, disease free survival; in patients with centrally reviewed tumors with a Gleason score of 8 to 10 there was a difference in survival in favor of the adjuvant goserelin arm. In protocol 92-02, patients with T2c-T4 tumors received goserelin and flutamide two months before and two months during radiation and were randomized to no further therapy or to 24 additional months of goserelin alone (LTAS). The LTAS arm significantly improved the disease free survival, local control, time to distant metastases, time to biochemical failure and showed a favorable trend for disease specific survival. In trial 94-13 the benefits of whole pelvis radiotherapy are manifested when HT is given before and during RT. EORTC trial 22861 has shown that androgen suppression with goserelin given during and for 3 years after external irradiation improves disease free and overall survival whatever the Gleason score is. EORTC trial 22961 closed in 2001, compared surveillance to hormonotherapy with triptoreline for 2·5 years after external irradiation and 6 months of combined androgen blockade. It is now possible to modulate the duration of hormonotherapy