FECS Presidential Session: FECS/EJC Award Lectures

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MSI derived frameshift mutations represent novel tumor specific antigens

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Microsatellite instability (MSI) caused by defective DNA mismatch repair (MMR) is a hallmark of hereditary non-polyposis colorectal cancers (HNPCC) but also occurs in about 15% of sporadic tumors. If instability affects microsatellites in coding regions, translational frameshifts lead to truncated proteins often marked by unique frameshift peptide sequences at their C-terminus. Since MSI tumors show enhanced lymphocytic infiltration and our previous analysis identified numerous coding mono- and dinucleotide repeat bearing candidate genes as targets of genetic instability, we examined the role of frameshift peptides in triggering cellular immune responses. Using peptide pulsed autologous CD40-activated B cells we have generated cytotoxic T lymphocytes (CTLs) that specifically recognize HLA-A2.1-restricted peptides derived from frameshift sequences. Among 16 frameshift peptides predicted from mutations in 8 different genes, 3 peptides conferred specific lysis of target cells exogenously loaded with cognate peptide. One peptide derived from a (-1) frameshift mutation in the TGF-betaIIR gene gave rise to a CTL bulk culture capable to lyse the MSI colorectal cancer cell line HCT116, carrying this frameshift mutation. Given the huge number of human coding microsatellites and assuming only a fraction being mutated and encoding immunologically relevant peptides in MSI tumors, frameshift protein sequences represent a novel subclass of tumor specific antigens. It is tempting to speculate that a frameshift peptide directed vaccination approach not only could offer new treatment modalities for existing MSI tumors but also might benefit asymptomatic at-risk individuals in HNPCC families by a prophylactic vaccination strategy.

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Results of EORTC phase III trial 22931 comparing, postoperatively, radiotherapy (RT) to concurrent chemo-radiotherapy (RT-CT) with high dose cisplatin in locally advanced head and neck (H&N) carcinomas (SCC)

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Purpose: To determine if, postoperatively, the combination of high dose cisplatin to RT significantly alter disease outcome in high risk SCC from oral cavity, oropharynx, larynx or hypopharynx, as compared to RT alone.

Patients (Pts) and Methods: From 1994 till 2000, 334 pts were randomly assigned to either RT (66 Gy/33 fr/6.5 wks - arm 1), or RT-CT (same RT combined to cisplatin, 100 mg/sqm, D1, 22 and 43 - arm 2).

Results: RT was completed on schedule in 73.9% of the cases whilst in arm 2, 29.5% of the patients did not receive the 3rd course of chemotherapy. At a median follow-up (FU) of 34 months, 3-year estimates are presented in the table. As for acute toxicity, grade 3-4 functional mucosal reactions (FMR) were significantly more frequent in arm 2, (44.5% vs 21.3%; p: 0.0004). There was no difference in objective mucosal reactions (OMR) between the 2 arms (p: 0.211). Grade 3-4 chemotherapy-related acute toxicity was found in 10.9% (granulocytopenia) and 1.9% (thrombocytopenia) of the cases.

Endpoints	RT (%)	RT-CT (%)	P value
Disease-free survival (DFS)	41	59	0.0096
Overall survival (OS)	49	65	0.0057
Time to progression (TTP)	44	66	0.0016
Local control (LC)	64	83	0.0014

Conclusions: As compared to RT alone, concurrent RT-CT with high dose cisplatin significantly increases DFS, OS, TTP and LC in pts with high risk H&N SCC after surgery. Although FMR are more frequent during RT-CT, the incidence of severe OMR is not significantly different between the 2 arms. Longer FU is needed to estimate accurately late complication, distant metastasis and second primary tumor rates.

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Treatment decisions in older patients with colorectal cancer: the role of age and functional status

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Purpose: It has been suggested that cancer in the elderly is badly treated and that criteria other than chronological age should form the basis for treatment decisions. In this study we assessed a broad range of functional indicators in older patients with colorectal cancer to discover whether age per se was a factor in these decisions, and whether functional status was in any way associated with treatment received.

Methods: 337 patients aged 58–95 years were interviewed before and after treatment for colorectal cancer using the OARS multidimensional functional assessment questionnaire, Rotterdam Symptom Checklist, and semi-structured interviews. Qualitative interviews were conducted with 15 consultant medical & surgical staff and 20 nursing staff in the 6 study centres. Data from patient questionnaires were analysed statistically using both univariate and multivariate techniques. Interviews with staff were analysed using the QSR*NUDIST software package.

Results: In this paper, we report associations between pre-treatment variables and treatment received, and present findings from interviews with staff. Older patients with Duke's C colorectal cancer (particularly those aged 75+) were less likely to receive adjuvant chemotherapy, although chemotherapy is regarded as standard treatment for this stage of the disease ($p = 0.001$, trend). In addition Duke's B & C patients who did receive adjuvant chemotherapy were found to be less impaired in social resources (quality/no. of relationships, availability of help during illness) ($p = 0.02$), as were Duke's C patients when analysed as a separate group ($p = 0.06$). Evidence from interviews with clinicians suggests that perceptions of older age discourage the use of adjuvant chemotherapy in older patients. Interviews with nurses raise important questions about the effects of authority and ownership of knowledge on treatment choices, and help to define the social context in which treatment decisions take place.

Conclusion: Older people in the UK are known to be treated differently in a number of ways because of their age. The suggestion in this study that chronological age and level of social resources, as well as clinical factors, are important influences on decisions about adjuvant chemotherapy in patients with colorectal cancer deserves further investigation and action to prevent inequities in health care provision.