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PD-L1 and PD-L2 genetic alterations define classical Hodgkin lymphoma and predict outcome

Roemer MG, Advani RH, Ligon AH, et al. Journal of Clinical Oncology, 2016; Aug 10;34(23):2690-7.

Purpose: Classical Hodgkin lymphomas (cHLs) include small numbers of malignant Reed-Sternberg cells within an extensive, but ineffective, inflammatory/immune cell infiltrate. In cHL, chromosome 9p24.1/PD-L1/PD-L2 alterations increase the abundance of the PD-1 ligands, PD-L1 and PD-L2, and their further induction through Janus kinase 2-signal transducers and activators of transcription signaling. The unique composition of cHL limits its analysis with high-throughput genomic assays. Therefore, the precise incidence, nature and prognostic significance of PD-L1/PD-L2 alterations in cHL remain undefined.

Methods: A fluorescent in situ hybridisation (FISH) assay was used to evaluate CD274/PD-L1 and PDCD1LG2/PD-L2 alterations in 108 biopsy specimens from patients with newly diagnosed cHL treated with the Stanford V regimen and had long-term follow-up. In each case, the frequency and magnitude of 9p24.1 alterations-polysomy, copy gain, and amplification-were determined, and the expression of PD-L1 and PD-L2 was assessed by immunohistochemistry, as also the association of 9p24.1 alterations with clinical parameters. These included stage (early stage I/II favourable risk, early stage unfavourable risk,advanced stage [AS] III/IV) and progression-free survival (PFS).

Results: 97% percent of the cHLs had concordant alterations of the PD-L1 and PD-L2 loci (polysomy, 5% [5 of 108]; copy gain, 56% [61 of 108]; amplification, 36% [39 of 108]). There was an association between PD-L1 protein expression and relative genetic alterations in this series. PFS was significantly shorter for patients with 9p24.1 amplification, and the incidence of 9p24.1 amplification was increased in patients with AS cHL.

Conclusions: PD-L1/PD-L2 alterations are a defining feature of cHL. Amplification of 9p24.1 is more common in patients with AS disease, and is associated with shorter PFS in this series. Further analyses of 9p24.1 alterations in patients treated with standard cHL induction regimens or checkpoint blockade are warranted.

Reviewer's comments: The treatment of classical Hodgkin lymphoma (cHL), particularly advanced stage disease, was revolutionised by the application of multi-agent cytotoxic chemotherapy regimens starting with Bonadonna's MOPP (mechlorethamine, vincristine, procarbazine and prednisone) in the 1970's up to the currently accepted standard-of-care ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine). However, targeted therapy (e.g. small molecule tyrosine kinase inhibitors) and monoclonal antibody-based therapy (with the exception of the anti-CD-30 chemotherapy drug conjugate brentuximab) made a rather limited impact thus far in contrast to many solid cancers. The long-term toxicities of intensive chemotherapy remain a concern. The unique histopathology of cHL – very infrequent neoplastic, malignant Hodgkin-Reed-Sternberg cells in a background of a number of immune cells – might suggest that immunotherapy to re-programme the cells of the immune penumbra to a more immune-permissive phenotype could have a role. Unlike solid cancers, haematological malignancies exhibit far more frequent genetic aberrations at the chromosomal level and this interesting paper demonstrates that almost all cases of cHL (predominantly early stage, nodular sclerosis subtype, non-bulky without B symptoms) showed copy-gain, amplification or rearrangement of the chromosome 9p24.1 encoding PD-L1 and L2. Malignant HRS cells expressed PD-L1/2 at the protein level, with evidence of activation of the JAK-STAT pathway. EBV-positive cases had stronger PD-L1 expression in keeping with the immunosuppressive effect of the virus. PD-L1/2 genetic amplification occurring more frequently in patients with advanced stage disease was associated with poorer progression-free survival in early-stage unfavourable and advanced stage patients. With the marked clinical efficacy of the anti-PD-1 antibody, nivolumab, already found in patients with advanced refractory cHL, these intriguing data suggest that the management of advanced cHL might be optimised by the use of PD-L1/2 genetic amplification as a biomarker to help early selection of patients whose outcome with conventional cytotoxic chemotherapy is poor and who might benefit from first-line immune checkpoint blockade. – AR

Effect of pathologic tumour Response and Nodal Status on Survival in the Medical Research Council Adjuvant Gastric Infusional Chemotherapy Trial

Smyth EC, Fassan M, Cunningham D, et al. Journal of Clinical Oncology. 2016 Aug 10;34(23):2721-7.

Purpose: The Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial established perioperative epirubicin, cisplatin and fluorouracil chemotherapy as a standard of care for patients with resectable esophagogastric cancer. However, identification of patients at risk for relapse remains challenging. We investigated whether pathologic response and lymph node status after neoadjuvant chemotherapy are prognostic in patients treated in the MAGIC trial.

Materials and methods: Pathologic regression was assessed in resection specimens by two independent pathologists using the Mandard tumour regression grading system (TRG). Differences in overall survival (OS) according to TRG were assessed using the Kaplan-Meier method and compared using the log-rank test. Univariate and multivariate analyses using the Cox proportional hazards method established the relationships between TRG, clinical-pathologic variables, and OS.

Results: 330 resection specimens were analysed. In chemotherapy-treated patients with a TRG of 1 or 2, median OS was not reached, whereas for patients with a TRG of 3, 4, or 5, median OS was 20.47 months. By univariate analysis, high TRG and lymph node metastases were negatively related to survival (Mandard TRG 3, 4, or 5: hazard ratio [HR], 1.94; 95% CI, 1.11 to 3.39; P = .0209; lymph node metastases: HR, 3.63; 95% CI, 1.88 to 7.0; P<0.001). On multivariate analysis, only lymph node status was independently predictive of OS (HR, 3.36; 95% CI, 1.70 to 6.63; P<0.001).

Conclusions: Lymph node metastases but not pathologic response to chemotherapy was the only independent predictor of survival after treatment plus resection in the MAGIC trial. Prospective evaluation of whether omitting postoperative chemotherapy and/or switching to a noncross-resistant regimen in patients with lymph node-positive disease whose tumor did not respond to preoperative epirubicin, cisplatin and fluorouracil may be appropriate.

Reviewer's comments: Upper gastrointestinal cancer remains a significant global healthcare challenge; although the incidence of gastric cancer is falling, that of oesophageal and gastro-oesophageal junctional adenocarcinomas is rising, possibly related to increasing rates of obesity and gastro-oesophageal reflux. The current standard of care for surgically resectable lower oesophageal, junctional and gastric cancers is surgery and perioperative chemotherapy based on the phase III randomised study MAGIC (surgery alone versus surgery plus epirubicin, cisplatin and 5FU chemotherapy), which demonstrated that perioperative chemotherapy was safe and not associated with increased surgical complications or surgical mortality, with an improvement in rates of five-year overall survival from 23 to 36% with chemotherapy. However, just under two-thirds of the patients will die from their disease and therefore further improvements in the treatment must be actively sought. This paper describes the relationship between the degree of pathologic tumour regression (as assessed by the Mandard system in which 1 represents no viable tumour cells and 5 represents viable tumour with no regression/fibrosis) after three cycles of ECF chemotherapy and the overall survival of the patients. Regardless of loco-regional lymph node status, patients with pathologic response to chemotherapy had a five-year survival rate almost twice that of those without a response (59 v 29%). Of particular interest, the survival curves stratified by nodal status and degree of chemotherapy-induced tumour regression suggested that long-term survival was extremely unlikely in node-positive patients without tumour regression. Further work will be required to determine if these patients should receive alternative (perhaps taxane- or irinotecan-based) chemotherapy regimens postoperatively, or whether radiation therapy should be included in their treatment. It will be interesting to see if metabolic imaging (i.e. CT-PET scan), or even biopsy after 2 cycles of chemotherapy, may help in making these decisions. – AR

New England Journal of Medicine

Extending aromatase-inhibitor adjuvant therapy to 10 years

Goss PE, Ingle JN, Pritchard KI, et al.
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Background: Treatment with an aromatase inhibitor for five years as up-front monotherapy or after tamoxifen is the treatment of choice for hormone-receptor–positive early breast cancer in post-menopausal women. Extending treatment with an aromatase inhibitor to 10 years may further reduce the risk of breast-cancer recurrence.

Methods: We conducted a double-blind, placebo-controlled trial to assess the effect of the extended use of letrozole for an additional five years. Our primary end point was disease-free survival.

Results: We enrolled 1,918 women. After a median follow-up of 6.3 years, there were 165 cases involving disease recurrence or the occurrence of contralateral breast cancer (67 with letrozole and 98 with placebo) and 200 deaths (100 in each group). The five-year disease-free survival rate was 95% (95% confidence interval [CI], 93 to 96) with letrozole and 91% (95% CI; 89 to 93) with placebo (hazard ratio for disease recurrence or the occurrence of contralateral breast cancer, 0.66; P=0.01 by a two-sided log-rank test stratified according to nodal status, prior adjuvant chemotherapy, the interval from the last dose of aromatase-inhibitor therapy, and the duration of treatment with tamoxifen). The five-year overall survival was 93% (95% CI, 92 to 95) with letrozole and 94% (95% CI, 92 to 95) with placebo (hazard ratio, 0.97; P=0.83). The annual incidence rate of contralateral breast cancer in the letrozole group was 0.21% (95% CI, 0.10 to 0.32), and the rate in the placebo group was 0.49% (95% CI, 0.32 to 0.67) (hazard ratio, 0.42; P=0.007). Bone-related toxic effects occurred more frequently among patients receiving letrozole than those receiving placebo, including a higher incidence of bone pain, bone fractures, and new-onset osteoporosis. No significant differences between letrozole and placebo occurred in scores on most subscales measuring quality of life.

Conclusion: The extension of treatment with an adjuvant aromatase inhibitor to 10 years resulted in significantly higher rates of disease-free survival and a lower incidence of contralateral breast cancer than those with placebo, but the rate of overall survival was not higher with the aromatase inhibitor than with placebo. (Funded by the Canadian Cancer Society and others; ClinicalTrials.gov numbers, NCT00003140 and NCT00754845.)

Reviewer's Comments: Extended adjuvant endocrine therapy in oestrogen receptor-positive breast cancer patients seems to provide extra benefit compared to the current standard of five years of adjuvant endocrine therapy. The 1995 NCI guidelines recommending five years of adjuvant tamoxifen where based on the results of a seven-year interim analysis of the NSABP-14 trial outcome (adjuvant tamoxifen for five vs ten years). More recently, the ATLAS and aTTOM trial data showing a 4% of incremental benefit for 10 years of tamoxifen compared with current standard five years (HR=0.80) refuted the NSABP-14 recommendation. Based on these extended endocrine trial results, many clinicians have already started offering 10 years of adjuvant tamoxifen to women with breast cancer at high risk of relapse. The definition of so-called high risk remains complex. Results of the joint analysis of the TEXT and SOFT salvage trials added support to extended endocrine manipulation in a subset of breast cancer population.

Almost all the previously reported randomised trials on duration of life included tamoxifen, but MA.17R study is unique in the sense that its result provides evidence on the use of an aromatase inhibitor for 10 years or more. After a median follow-up of 6.3 years, five-year disease-free survival was 95% with letrozole and 91% with placebo. There were 55 recurrences in the 10 years compared to 68 in the five years of letrozole. Closer scrutiny shows that, of

those recurrences, the majority gaining benefit of this risk reduction was in contralateral breast cancer (13 with 10 years vs 31 with five years of letrozole). As far as distant recurrences are concerned, there were only 11 more in the placebo arm, of which 9 were in the bone. The trade-off was a small increase in the rates of adverse skeletal events such as osteoporosis and fractures (14 vs 9%; p=0.001). There were relatively small deteriorations over time in the global quality of life, as assessed from summary scores on the mental and physical scales of the 36-item Short Form Health Survey (SF-36). Perhaps the implementation of bone-health maintenance strategies could abrogate the risk of fracture, even in patients receiving long-term treatment with an aromatase inhibitor.

The beneficial effects of mainly disease-free survival with a favourable toxicity profile for continuing the letrozole for additional five years are reassuring. However, these findings will pose direct challenge to clinicians and patients alike. In this trial, the greatest effect with extended duration was risk reduction of new contra-lateral breast cancer. Chemo-prevention remains a controversial topic because of its doubtful value. Like many breast cancer prevention studies, the favourable side effects in MA.17R trial are most likely due to the self-selection of women who did not get side effects during the initial five years of adjuvant letrozole.

These results are like a roller coaster; the data are not definitive and do not provide indisputable evidence of the drug to be incorporated in standard guidelines. At the post-plenary discussion of the results, Paul Goss – who presented these data at ASCO 2016 – hesitated to advocate for the use of letrozole for an additional five years. With relatively modest benefit from extended therapy, patient selection to tailor the duration of endocrine therapy has to take central stage. We need to develop tools for personalised medicine. In the era of molecular genomic profiling, the new guidelines have to incorporate this technique to select appropriate individuals who are at a higher risk of relapse for extended endocrine therapy – SU

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