Highlights in haematological cancer from the 2016 annual meeting of the American Society of Clinical Oncology (ASCO)

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From June 3rd till June 6th, Chicago again formed the background for the biggest cancer congress in the world. Notwithstanding the fact that solid tumours remain the main focus of the annual meeting of the American Society of Clinical Oncology (ASCO), the meeting program also included some interesting lectures on haematological malignancies. The aim of this report is not to discuss all these studies, but will address some of the key presentations on haematological cancer from ASCO 2016. For a more complete overview we would like to refer to the congress website, where all abstracts and a plethora of webcasts can be found.

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Daratumumab combination associated with unprecedented PFS benefit in multiple myeloma

The CASTOR study included 498 patients with recurrent or refractory multiple myeloma who were randomised 1:1 to receive 8 cycles of bortezomib/dexamethasone with or without 16 mg/kg of daratumumab. Bortezomib was administered subcutaneously at 1.3 mg/m^2 on days 1, 4, 8, and 11 of each 21-day cycle for a maximum of 8 cycles. Patients received 20 mg of oral dexamethasone on days 1, 2, 4, 5, 8, 9, 11, and 12 of the first 8 bortezomib treatment cycles. Patients in the daratumumab group were administered an intravenous (IV) infusion of the antibody at 16 mg/kg weekly for the first 3 cycles, on day 1 of cycles 4 to 9, and then every 4 weeks. Treatment was administered until disease progression or unacceptable toxicity. Patients in the trial had received a median of 2 prior lines of therapy (range, 1-10) and 66% had received prior bortezomib, 76% has received prior immunomodulatory drugs (IMiDs), and 48% had received prior proteasome inhibitors and IMiDs. Thirty-three percent were IMiD-refractory and 32% were refractory to the last line of prior therapy.[1]

The median progression-free survival (PFS) was 7.5 months in the standard treatment arm and was not yet reached in the daratumumab arm (HR [95%CI]: 0.31 [0.18-0.52]; p<0.0001) (*Figure 1*). The overall response rates were 83% and 63% (p<0.0001) in the experimental and control arms, respectively. Nineteen percent of patients in the daratumumab arm had a complete response (CR) or better and 59% of patients had a very good partial response (VGPR) or better compared with 9% of patients experiencing a CR and 29% experiencing a VGPR in the control arm (p= 0.0012, p<0.0001, respectively).[1]

The most common treatment-emergent adverse events were thrombocytopenia, which occurred in 59% of patients in the daratumumab arm versus 44% in the bortezomib/dexamethasone arm; sensory peripheral neuropathy, which occurred in 47% and 38% of patients

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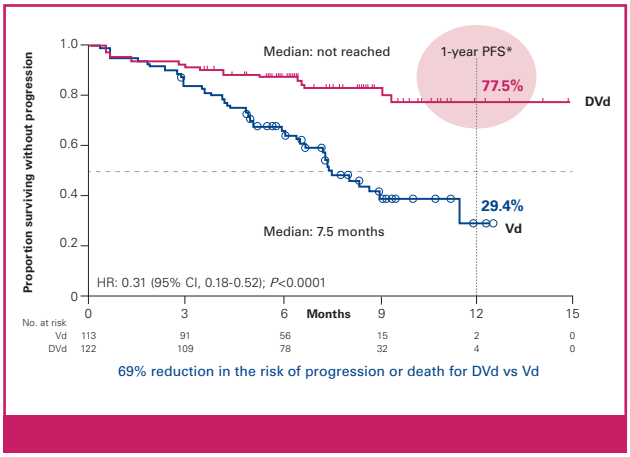

Figure 1. Progression-free survival in the phase III CASTOR study.[1] *DVd=daratumumab, bortezomib and dexamethasone, Vd=bortezomib and dexamethasone.*

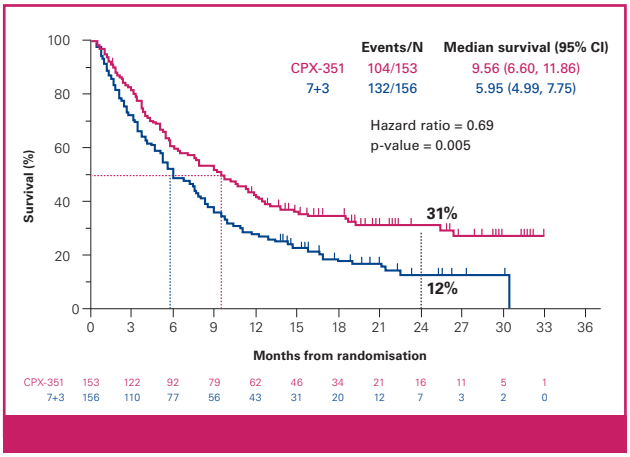

Figure 2. CPX-351 prolongs the overall survival in patients with acute myeloid leukaemia.[2]

in the experimental and control arms, respectively; diarrhoea, which occurred in 32% and 22% of patients in each arm, respectively, and anaemia, which occurred in 26% and 31% of patients in each arm, respectively. This higher proportion of thrombocytopenia and peripheral neuropathy in the daratumumab arm was most likely due to the fact that patients in that arm were exposed to bortezomib longer in comparison with the control arm, which had a higher proportion of early progressions. In total, 7% of patients in the daratumumab arm discontinued treatment due to adverse events versus 9% of patients receiving bortezomib/dexamethasone alone. Infusion-related reactions (IRRs) were experienced by 45% of patients in the study overall. Nine percent were grade 3, there were no grade 4 IRRs, and 98% occurred during the first infusion.[1]

Final phase III data confirm the survival benefit of CPX-351 in acute myeloid leukaemia

CPX-351 is a liposomal formulation containing a fixed combination of cytarabine and daunorubicin in a 5:1 molar ratio that was developed using a system known as 'CombiPlex', which was developed by Celator. This platform is meant to improve upon existing therapies through in vitro studies that illuminate an optimal molar ratio for combinations. The presented randomised, controlled phase III trial included 309 acute myeloid leukaemia (AML) patients, between 60 and 75 years of age. Patients enrolled in the study were split into either an age group consisting of patients between the ages of 60-69 or from 70-75 and were further stratified based on AML type. Patients had either therapy-related AML, AML with a history of MDS with and without prior hypomethylating agent-based therapy, AML with a history of CMML, or de novo AML with MDS karyotype. Approximately 62% of patients in each arm were male. In the CPX-351 arm, 90.2% of patients had an ECOG PS of 0 or 1, with 85.9% of patients in the 7+3 regimen arm having an ECOG PS of 0 or 1. The proportion of patients with an ECOG PS of 2 was 9.8% and 14.1%, respectively.

Patients were randomised in a 1:1 ratio to receive either CPX-351 (N=153) or 7+3 (N=156). Those receiving CPX-351 were given a first induction of 100 U/m^2 on days 1, 3, and 5. Patients in the control arm received daily cytarabine 100 mg/m^2 for 7 days, followed by daunorubicin 60 mg/m^2 on days 1, 2, and 3. Second induction for patients enrolled in the CPX-351 arm was 100 U/m^2 on days 1 and 3, while patients receiving conventional cytarabine and daunorubicin were given cytarabine 100 mg/m^2 daily for 5 days with daunorubicin 60 mg/m^2 on days 1 and 2. At 12 months, 41.5% of patients enrolled in the CPX-351 arm remained alive versus 27.6% in the 7+3 arm. At 24 months, 31.1% of patients enrolled in the CPX-351 arm of the study remained alive compared with 12.3% with 7+3. The median overall survival (OS) was 9.56 months with CPX-351 compared to 5.95 months with 7+3 (HR: 0.69; p=0.005) (*Figure 2*).[2]

The median event-free survival was 2.53 months with CPX-351 versus 1.31 months with 7+3 (HR: 0.74; p=0.021). Induction response rates (complete remission [CR] plus CR with incomplete hematologic recovery [CRi]) were 47.7% for CPX-351 versus 33.3% for 7+3, yielding a relative benefit of 43.2% with the investi-

gational treatment (p=0.016). For CR alone, the rates were 37.3% and 25.6%, between CPX-351 and 7+3, respectively (p=0.04).

Patients who achieved a CR or CRi were eligible to receive consolidation chemotherapy. In the investigational therapy arm, consolidation CPX-351 was administered at 65 U/m^2 on days 1 and 3. In the control arm, consolidation therapy consisted of daily cytarabine at 100 mg/m^2 for 5 days and daunorubicin at 60 mg/m^2 on days 1 and 2 (5+2).[2]

As a primary measurement of toxicity and safety, the researchers analysed the early mortality rate. There appeared to be a moderately decreased risk of early mortality at both 30 days and 60 days favouring CPX-351 compared to 7+3. The rates of grade 3 to 5 non-haematologic adverse events (AEs) were similar between the 2 arms. Common grade 3 to 5 AEs occurring in the 2 arms included febrile neutropenia (68% with CPX-351 vs. 71% with 7+3), pneumonia (20% vs. 15%), hypoxia (13% vs. 15%), sepsis (9% vs. 7%), hypertension (10% vs. 5%), respiratory failure (7% each), fatigue (7% vs. 6%), bacteraemia (10% vs. 2%), and decreased ejection fraction (5% each). As a measure of haematologic toxicity, the researchers assessed blood count recovery in patients achieving a CR or CRi. Patients who received either 1 or 2 inductions of CPX-351 had an approximately 7-day delay in count recovery of neutrophils and platelets compared with the 7+3 group. Of note, no increased incidence of early death as a function of delayed count recovery was seen.[2]

The researchers also assessed outcomes specifically among patients who underwent haematopoietic stem cell transplantation (HSCT). About one-third of patients underwent HSCT during the study and these patients were well-balanced in baseline characteristics between the 2 arms. A sensitivity analysis at the time of transplant showed that there was a trend toward improved OS in patients who received CPX-351 compared with 7+3. The median OS was 7.75 months versus 5.55 months, respectively (HR 0.81; p=0.165).[2]

Promising results with first-line venetoclax and decitabine/azacitidine in acute myeloid leukaemia

Venetoclax is a potent, orally bioavailable BCL-2 inhibitor with single-agent activity in relapsed/refractory AML patients, displaying synergistic activity with hypomethylating agents in preclinical studies. A study, presented at ASCO 2016, evaluated venetoclax plus decitabine or azacitidine in treatment-naive AML patients, aged 65 or more. In total, 39 untreated AML patients who were not eligible for standard induction therapy received decitabine (arm A: 20 mg/m^2 IV) daily on days 1-5, or azacitidine (arm B: 75 mg/m^2; subcutaneous or IV) daily on days 1-7 of each 28-day cycle in combination with once-daily continuous oral venetoclax.

No dose-limiting toxicities were reported and there was no evidence of tumour lysis. The most common serious adverse events were neutropenia and febrile neutropenia. The overall ≥grade 3 infection rate was 31% (27% bacterial, 4% fungal). The reported overall response rate (ORR) was 62% (CR or CRi in 60%) with a median time to CR/CRi of 1 months and a median duration of response of 8.4 months. No differences were seen between the azacitidine and the decitabine arms.[3]

Nivolumab for relapsed or refractory Hodgkin lymphoma

Most cases of classical Hodgkin lymphoma (cHL) overexpress PD-1 ligands and have shown high rates of response to PD-1 blockade. Younes and colleagues conducted a multicentre phase II trial involving 80 patients who had relapsed after autologous SCT and after receiving brentuximab vedotin who were treated with nivolumab once every 14 days.[4]

The ORR in this study was 66% (CR, 9%), and was 72% in brentuximab vedotin non-responders. In total, 6 responding patients proceeded to a second SCT. The PFS rate at 6 months was 77%.

One treatment-related death occurred, 25% of patients had grade 3 or 4 toxicity, and 26% had grade 1 or 2 immune toxicities. Of note, nivolumab was recently approved in the U.S. for this population of relapsed or refractory cHL.[4]

Bortezomib for high-risk follicular lymphoma

Evens and colleagues conducted a randomised phase II trial to determine the effect of adding bortezomib to bendamustine-rituximab (BR) in 222 treatment-naive patients with previously untreated high-risk follicular lymphoma (defined as high tumour burden by GELF or FLIPI score 3 to 5). Patients were randomised 1:2:2 to BR for 6 cycles followed by maintenance rituximab (MR) for 2 years versus BR plus bortezomib (BVR) for 6 cycles followed by MR for 2 years versus BR for 6 cycles followed by MR for 2 years plus lenalidomide for 1 year.[5]

The ORR in this trial was similar with induction BVR and BR (91% and 90%, respectively). However, CR

rates were improved with BVR compared to BR (74% vs. 58%; p=0.016). Most patients in each treatment arm (86%) completed all 6 cycles of induction. Whether the higher CR rate with BVR translates to longer-term benefit, and whether adding lenalidomide to MR improves outcomes, will require longer follow-up.[5]

Maintenance rituximab for mantle cell lymphoma

Maintenance rituximab is a standard of care following induction therapy with R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone). Rummel et al. conducted a multicentre, prospective, randomised, phase II study to test the role of maintenance rituximab every two months for two years versus observation following six cycles of bendamustine-rituximab in 120 previously untreated mantle cell lymphoma patients who achieved a partial or complete response.[6]

At a median follow-up of 4.5 years, no differences were observed between the two arms in either PFS or OS. Caveats of this study include the relatively small number of patients and the need for longer follow-up. In addition to this, an analysis of minimal residual disease (MRD) in bone marrow and peripheral blood following induction may better define those who would benefit from maintenance rituximab or consolidation strategies.

Maintaining a durable remission in CML patients without a tyrosine kinase inhibitor

Hochhaus et al. presented the data of the ENESTfreedom study. This study investigated the effect of discontinuing treatment with the tyrosine kinase inhibitor nilotinib in CML patients who achieved a deep molecular response on nilotinib. In the consolidation phase of the ENESTfreedom study, 215 patients were treated with nilotinib for 52 weeks. Patients with a durable molecular response then moved to the treatment-free remission (TFR) phase of the study. In this study a sustained deep molecular response was defined as an $MR^{4.5}$ in the final analysis, not a single evaluation worse than an MR^4 and not more than 2 evaluations between MR^4 and $MR^{4.5}$. When the response was lost in the TFR phase, nilotinib was restarted.[7]

In total, 98 of the 190 patients who entered the TFR phase remained in TFR after 48 weeks (51.6%; 95% CI: 44.2%-58.9%). This finding was however not significant as the lower boundary of the confidence interval was lower than the pre-defined boundary for significance of 50%. In total, nilotinib was restarted in 86 patients and 85 of them (98.8%) were able to re-establish a MMR. In 76 of the 'restart' patients (88.4%) an $MR^{4.5}$ was achieved.[7]

As compared with the consolidation phase of the trial, the TFR phase was characterized by a lower incidence of many of the nilotinib-associated adverse events. The researchers did however observe a higher rate of musculoskeletal pain in the TFR phase. These adverse events were however mostly low grade. This finding is in line with the previously described TKI withdrawal syndrome.

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