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Oxaliplatin in lymphoma

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To day, 50 to 60% of patients with diffuse large cell lymphoma (DLCL) are cured by conventional chemotherapy but the outcome of patients who either fail to respond or relapse remains very poor. High dose therapy (HDT) followed by autologous stem cell support (ASCS) has become the standard option for such patients in failure. Complete response rates to first-line treatment with anthracyclin-containing CHOP or CHOP-derived regimens are about 70%, with 5% toxic deaths, 10–15% partial responses and 10% *primary failure*. Among failures, relapses occurring in patients who first reached complete response are the most frequent event and despite salvage treatment have a 5y-survival of 30%–40%. Late relapses (occurring after one year of remission duration) have a better outcome than early relapses whose prognosis is close to that of primary failures.

Salvage-regimens

Platinum containing regimens, such as DHAP, ICE and ESHAP are used prior to high-dose chemotherapy with ASCS in an attempt to obtain complete response. More recently, the monoclonal anti-CD20 antibody rituximab used as single agent has shown interesting activity with a 30% objective response rate in patients with aggressive B-cell lymphoma in failure, thereby encouraging its use in combination with chemotherapy. As a matter of fact, such salvage regimens are the first part of a strategy which will ultimately incorporate, whenever feasible, a final step of HDT/ASCS. These combinations give response rates in the 40–60% range but result in severe myelosuppression, renal toxicity and peripheral neuropathy.

Furthermore, even though high-dose chemotherapy with ASCS is now an established consolidation treatment for chemosensitive relapses, there is a large proportion of patients who are unable to receive high-dose chemotherapy because of age, previous HDT/ASCS in first-line treatment and co-morbidities. In addition,

many patients relapse after stem cell transplantation. For these patients there is no standard salvage chemotherapy.

Oxaliplatin

Oxaliplatin is a 3rd generation platinum (trans-1-1,2-diaminocyclohexane oxalato-platin) compound which inhibits DNA replication by cross-linked DNA adduct formation. Oxaliplatin is a recently introduced platinum derivative mainly used in colorectal cancer. At conventional doses, it is devoid of any renal or auditive toxicity, but is associated with significant acute and chronic peripheral neuropathy.

Two phase II studies of single-agent oxaliplatin in heavily pretreated lymphoma patients have been reported^{1,2} showing an ORR of 40% (n=22) and 27% respectively (n=30). Responses occurred across various types of lymphoma. The apparently favorable toxicity profile of Oxaliplatin as compared to Cisplatin led to explore the substitution of one drug by the other inside the classical DHAP regimen. Two European phase II studies assessed the efficacy and safety of oxaliplatin substituted to cisplatin in the DHAox regimen (including Oxaliplatin 130 mg/m² at day 1 instead of Cisplatin) for refractory/relapsed lymphoma of various histologies.^{3,4} They reported ORR of 50% (n=24) and 73% (n=15), respectively. Treatment was associated with frequent (66–75%) albeit manageable grade 3–4 hematological toxicity.

Addition of rituximab to DHAox regimen has also been evaluated in a single institution study and data, although very preliminary, look promising.⁵

Oxaliplatin and gemcitabine have been shown separately to be active in relapsed or refractory NHL.^{1,2,6,7} The combination of these two drugs has been tested in a variety of solid tumors as well as in lymphomas and appear feasible and safe. Moreover, it has been assessed that gemcitabine-oxaliplatin combination displays supra-additive effects in human leukemia and colon-cancer cell lines.⁸

Based on these considerations, we designed an open-label phase II study of the combination of rituximab, gemcitabine and oxaliplatin in the treatment of patients with relapsed or refractory B-cell lymphoma. Patients included in this study were all treated at the Hematology department of the CHU Henri Mondor, Créteil, France. Were considered eligible all patients under 80 years with recurrent or refractory CD20 positive lymphoma not eligible for HDT/ASCS. From 2001, 40 patients have been treated with the R-GEMOx regimen.⁹

Rituximab was administered on day 1 at the dose of 375 mg/m² following the usual infusion-rate escalation protocol after premedication with 1 mg/m² IV methylprednisolone, 1 g oral acetaminophen and 6 mg oral dexchlorpheniramine in order to avoid infusion-related side effects. Gemcitabine was administered over 2 hours at a dose of 1,000 mg/m² in 500 mL normal saline on day 2. Administration of gemcitabine at a fixed dose rate of 10 mg/m²/min permits superior intracellular drug concentration compared to the usual 30 minute IV administration schedule. Oxaliplatin was administered after gemcitabine on day 2 at a dose of 100 mg/m² over 2 hours. Cycles were repeated every 15 days.

A complete blood count was performed on days 7, 10 and 14 of each treatment cycle to assess hematological toxicity, and patients underwent clinical examination and routine chemistry before each new cycle. No dose adjustment was planned according to hematological toxicity, but cycles were postponed until the absolute neutrophil count reached 1.0×10⁹/L and platelet counts 100×10⁹/L. The dose of oxaliplatin was planned to be adjusted according to the degree of peripheral neuropathy: the dose was to be reduced to 75 mg/m² in case of significant paresthesia lasting between 7 and 13 days after each administration, and oxaliplatin was to be omitted until improvement and

then restarted at 75 mg/m² in case of abnormal neurological examination or in case of significant paresthesia lasting for 14 days or more.

Patients were planned to undergo four treatment cycles before restaging. Patients showing a complete, complete-unconfirmed or partial response were planned to undergo four supplementary consolidation cycles.

Histological subtypes were: diffuse-large B cell lymphoma in 30 patients, follicular lymphoma in 7 and mantle cell lymphoma in 3 patients.

The overall response rate after 4 cycles was 85%. NCIC grade 3-4 neutropenia and thrombocytopenia were reported in 50% and 25% of the cycles, respectively. Seven patients developed a grade 4 infection during one cycle. There was no renal toxicity and no grade 3-4 neuropathy.

As of January 2005, 30 patients are alive, 19 in continuous complete remission, 8 with progressive disease and 3 were *on therapy*.

For the 34 responding patients, the median time to progression estimated by the Kaplan-Meier method was 20 months (range: 1.6 to > 33.5 months) and median duration of response was 18 months (range: 0.5 to >31.4 months).

The lack of nephrotoxicity gives oxaliplatin an important advantage over cisplatin. Oxaliplatin can be given to elderly patients and those with renal or cardiac impairment. It is easier to administer as does not require hyperhydration. Among the combinations, R-GEMOx has the convenience of being an outpatient regimen, as opposed to the current salvage therapies.

Based on these efficacy and safety data on oxaliplatin in lymphoma, this new regimen is now evaluated in an ongoing multicentric phase II study, led by the GELA, on refractory/first and second relapsed patients with diffuse large B-cell lymphoma non eligible for HDT/ASCS or having relapsed after transplantation.

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