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EVEROLIMUS IN RELAPSED HODGKIN LYMPHOMA, SOMETHING EXCITING OR A CASE OF CAVEAT mTOR?

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Hodgkin's disease (HD) is a rare form of cancer that predominantly affects young people with an incidence of approximately 3/100,000 in the Western World. SInce the advent of combination chemotherapy **[1]** this has proven to be a highly curable disease, however a significant number of patients presenting with HD will ultimately die from it. This includes young patients relapsing after salvage chemotherapy and transplantation and a proportion of elderly patients for whom conventional chemotherapy is not appropriate or well tolerated and where different approaches are needed. In this issue of the *American Journal of Hematology,* Johnston *et al* **[2]** describe the first clinical trial of the mTOR inhibitor everolimus in patients with relapsed / refractory HD.

Sirolimus (rapamycin) is a macrolide antibiotic that was developed and subsequently licensed as an immunosuppressive agent for use in solid organ transplantation. As part of the National Cancer Institute's Cancer Therapeutics Evaluation Programme (CTEP), rapamycin was shown to have anti-tumour effects demonstrable against a range of malignancies. Although the variable bioavailability of this agent made it pharmacologically unsuitable to be taken any further as an anti-cancer agent, a number of novel analogues (temsirolimus (CCI-779), everolimus (RAD 001) and deforolimus (AP 23573)) have been developed. These drugs work through inhibition of the mammalian target of rapamycin (mTOR). This is a serine/threonine kinase that has a key role in regulating cell cycle progression, cellular growth and protein synthesis through interactions with a number of signalling pathways including PI3K/AKT, bcr/abl, ras, TCL1 and membrane receptor tyrosine kinases **[3]**. The phosphatidylinositol 3-kinase/Akt/mTOR pathway is heavily dysregulated in haematological malignancies, including Hodgkin's disease **[4]** and provides a rationale for the use of mTOR inhibitors.

All of the 3 mTOR inhibitors have been trialled in various cancers **[5]** with the most extensive experience involving intra-venous temsirolimus **[6]**. The phase I studies with temsirolimus demonstrated activity in renal cell carcinoma **[7, 8]** and subsequent studies lead to its licensing for this indication **[9]**. In mantle cell lymphoma (MCL) two phase II trials demonstrated response rates of around 40% **[10, 11]** and a subsequent large randomised phase III trial showed a significant PFS advantage for temsirolimus over investigator choice single agent chemotherapy. This led on to a European license for this indication but the response rate in this multi-centre trial was only 22% **[12]**. In common, everolimus has a license in relapsed renal cell carcinoma **[13]** and *in vitro* appears active against MCL **[14]**. A phase II single agent study in this disease is on-going in Europe.

Johnston and colleagues describe the first trial of an mTOR inhibitor in Hodgkin's disease. This was a single centre phase II trial that evaluated a total of 19 patients as part of a larger study evaluating this drug in rarer forms of lymphoma. This was a representative population with a median age of 37 years, who were heavily pre-treated (median number of prior therapies of 6) and where the median TTP for their last therapy was 4 months. Using a daily oral dose of 10mg the observed ORR was 47% with a median duration of response of 7.1 months. This included 1 CR and 4 patients remain progression free at 12 months with 1 patient remaining on drug for over 3 years. However 74% patients experienced grade III/IV toxicity and half of all patients required dose reductions. Whilst haematological toxicity predominated, 5 patients (25%) experienced significant pulmonary toxicity, a side effect that has previously been observed in other studies involving both everolimus **[15]** and temsirolimus **[12]**.

Where does this take the therapy of HD? This study suggests that everolimus is an active agent in this disease but this requires further evaluation in a multi-centre setting. The difference in observed response rates with temsirolimus in mantle cell lymphoma between the phase II and phase III settings certainly warrant some caution. However within the larger trial of everolimus in rarer lymphomas, the efficacy in CLL/SLL

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(response rate of 18%) **[16]** is clearly inferior to that seen in HD suggesting this to be a suitable disease in which to explore this compound further. There is a real need for agents that can be given to patients who have exhausted conventional options in this disease and an oral agent is advantageous especially for the elderly patients. In one population based study of patients over 60 presenting with HD almost half of the patients died from progressive disease and almost all patients over 70 years did, even if it was localised at presentation **[17]**. The toxicity observed in the study from Johnston would be a cause for concern when expanding that experience to an older, frailer cohort of patients where arguably there is a greater need for such agents. If the response rates observed with everolimus are verified then a move to combination therapy would be the obvious next stage however, the unexplained pulmonary toxicity seen here, which has also been observed previously in renal cell carcinoma suggest that caution should be observed**[18]**. Despite the fact that the FDA have not approved any new drug for HD in 30 years there are a number of promising agents in development, including HDAC inhibitors, lenalidomide, anti-CD30 and other antibodies **[19]**. Whilst phase II single agent studies are a good place to start, it is essential that promising agents are moved into randomised phase III trials that compare them against established therapeutic options before they can safely and confidently moved into the clinic.

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