Mechanical and thermal sequences impact largely on thermo-mechanical fatigue of dies in a die casting operation. Innovative techniques to optimize the thermo-mechanical conditions of samples are major focus of researchers. This study investigates the typical thermal fatigue in die steel. Die surface initiation and crack propagation were stimulated by thermal and hardness gradients, acting on the contact surface layer. A design of experiments (DOE) was developed to analyze the effect of as-machined surface roughness and die casting parameters on thermal fatigue properties. The experimental data were assessed on a thermo-mechanical fatigue life assessment model, being assisted by response surface methodology (RSM). The eminent valuation was grounded on the crack length, hardness properties and surface roughness due to thermal fatigue. The results were analyzed using analysis of variance method. Parameter optimization was conducted using response surface methodology (RSM). Based on the model, the optimal results of 26.5 μm crack length, 3.114 μm surface roughness, and 306 HV0.5 hardness properties were produced.